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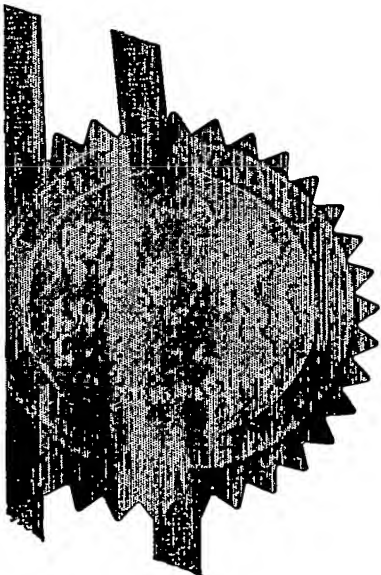
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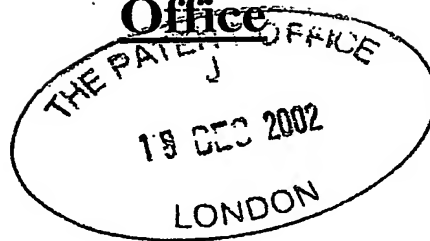
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T1569PV2

Patent application number

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19 DEC 2002

Full name, address and postcode of the or of each applicant (underline all surnames)

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Patents ADP number (if you know it)

00597799001 ✓

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

Title of the invention

Therapeutic agents

Name of your agent (if you have one)

Dr. J. Thompson

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Patents ADP number (if you know it)

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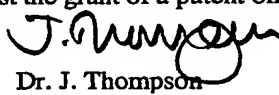


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Dr. J. Thompson

Date 19 December 2002

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THERAPEUTIC AGENTS

The present invention relates to a class of substituted pyridazine derivatives and to their use in therapy. More particularly, this invention is concerned with 4-phenylpyridazine analogues. These compounds are ligands for GABA_A receptors and are therefore useful in the therapy of deleterious neurological complaints.

Receptors for the major inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), are divided into two main classes: (1) GABA_A receptors, which are members of the ligand-gated ion channel superfamily; and (2) GABA_B receptors, which may be members of the G-protein linked receptor superfamily. Since the first cDNAs encoding individual GABA_A receptor subunits were cloned the number of known members of the mammalian family has grown to include at least six α subunits, four β subunits, three γ subunits, one δ subunit, one ϵ subunit and two ρ subunits.

Although knowledge of the diversity of the GABA_A receptor gene family represents a huge step forward in our understanding of this ligand-gated ion channel, insight into the extent of subtype diversity is still at an early stage. It has been indicated that an α subunit, a β subunit and a γ subunit constitute the minimum requirement for forming a fully functional GABA_A receptor expressed by transiently transfecting cDNAs into cells. As indicated above, δ , ϵ and ρ subunits also exist, but are present only to a minor extent in GABA_A receptor populations.

Studies of receptor size and visualisation by electron microscopy conclude that, like other members of the ligand-gated ion channel family, the native GABA_A receptor exists in pentameric form. The selection of at least one α , one β and one γ subunit from a repertoire of seventeen allows for the possible existence of more than 10,000 pentameric subunit combinations. Moreover, this calculation overlooks the additional permutations that would be possible if the arrangement of subunits

around the ion channel had no constraints (i.e. there could be 120 possible variants for a receptor composed of five different subunits).

Receptor subtype assemblies which do exist include, amongst many others, $\alpha 1\beta 2\gamma 2$, $\alpha 2\beta \gamma 1$, $\alpha 2\beta 2/3\gamma 2$, $\alpha 3\beta \gamma 2/3$, $\alpha 4\beta \delta$, $\alpha 5\beta 3\gamma 2/3$, $\alpha 6\beta \gamma 2$ and $\alpha 6\beta \delta$.

5 Subtype assemblies containing an $\alpha 1$ subunit are present in most areas of the brain and are thought to account for over 40% of GABA_A receptors in the rat. Subtype assemblies containing $\alpha 2$ and $\alpha 3$ subunits respectively are thought to account for about 25% and 17% of GABA_A receptors in the rat. Subtype assemblies containing an $\alpha 5$ subunit are expressed
10 predominantly in the hippocampus and cortex and are thought to represent about 4% of GABA_A receptors in the rat.

A characteristic property of all known GABA_A receptors is the presence of a number of modulatory sites, one of which is the benzodiazepine (BZ) binding site. The BZ binding site is the most explored
15 of the GABA_A receptor modulatory sites, and is the site through which anxiolytic drugs such as diazepam and temazepam exert their effect. Before the cloning of the GABA_A receptor gene family, the benzodiazepine binding site was historically subdivided into two subtypes, BZ1 and BZ2, on the basis of radioligand binding studies. The BZ1 subtype has been
20 shown to be pharmacologically equivalent to a GABA_A receptor comprising the $\alpha 1$ subunit in combination with a β subunit and $\gamma 2$. This is the most abundant GABA_A receptor subtype, and is believed to represent almost half of all GABA_A receptors in the brain.

Two other major populations are the $\alpha 2\beta \gamma 2$ and $\alpha 3\beta \gamma 2/3$ subtypes.
25 Together these constitute approximately a further 35% of the total GABA_A receptor repertoire. Pharmacologically this combination appears to be equivalent to the BZ2 subtype as defined previously by radioligand binding, although the BZ2 subtype may also include certain $\alpha 5$ -containing subtype assemblies. The physiological role of these subtypes has hitherto
30 been unclear because no sufficiently selective agonists or antagonists were known.

It is now believed that agents acting as BZ agonists at $\alpha 1\beta\gamma 2$, $\alpha 2\beta\gamma 2$ or $\alpha 3\beta\gamma 2$ subtypes will possess desirable anxiolytic properties. Compounds which are modulators of the benzodiazepine binding site of the GABA_A receptor by acting as BZ agonists are referred to hereinafter as "GABA_A receptor agonists". The $\alpha 1$ -selective GABA_A receptor agonists alpidem and zolpidem are clinically prescribed as hypnotic agents, suggesting that at least some of the sedation associated with known anxiolytic drugs which act at the BZ1 binding site is mediated through GABA_A receptors containing the $\alpha 1$ subunit. Accordingly, it is considered that GABA_A receptor agonists which interact more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with $\alpha 1$ will be effective in the treatment of anxiety with a reduced propensity to cause sedation. Moreover, agents which are inverse agonists of the $\alpha 5$ subunit are likely to be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease. Also, agents which are antagonists or inverse agonists at $\alpha 1$ might be employed to reverse sedation or hypnosis caused by $\alpha 1$ agonists.

The compounds of the present invention, being selective ligands for GABA_A receptors, are therefore of use in the treatment and/or prevention of a variety of disorders of the central nervous system. Such disorders include anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, animal and other phobias including social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic and acute stress disorder, and generalized or substance-induced anxiety disorder; neuroses; convulsions; migraine; depressive or bipolar disorders, for example single-episode or recurrent major depressive disorder, dysthymic disorder, bipolar I and bipolar II manic disorders, and cyclothymic disorder; psychotic disorders including schizophrenia; neurodegeneration arising from cerebral ischemia; attention deficit hyperactivity disorder; Tourette's syndrome;

speech disorders, including stuttering; and disorders of circadian rhythm, e.g. in subjects suffering from the effects of jet lag or shift work.

Further disorders for which selective ligands for GABA_A receptors may be of benefit include pain and nociception; emesis, including acute, 5 delayed and anticipatory emesis, in particular emesis induced by chemotherapy or radiation, as well as motion sickness, and post-operative nausea and vomiting; eating disorders including anorexia nervosa and bulimia nervosa; premenstrual syndrome; muscle spasm or spasticity, e.g. in paraplegic patients; hearing disorders, including tinnitus and age- 10 related hearing impairment; urinary incontinence; and the effects of substance abuse or dependency, including alcohol withdrawal. Selective ligands for GABA_A receptors may be beneficial in enhancing cognition, for example in subjects suffering from dementing conditions such as Alzheimer's disease; and may also be effective as pre-medication prior to 15 anaesthesia or minor procedures such as endoscopy, including gastric endoscopy.

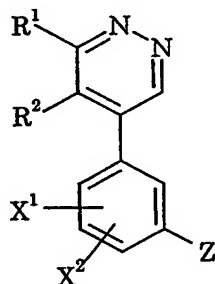
In addition, the compounds in accordance with the present invention may be useful as radioligands in assays for detecting compounds capable of binding to the human GABA_A receptor.

20 The present invention provides a class of pyridazine derivatives which possess desirable binding properties at various GABA_A receptor subtypes. The compounds in accordance with the present invention have good affinity as ligands for the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit of the human GABA_A receptor. The compounds of this invention may interact 25 more favourably with the $\alpha 2$ and/or $\alpha 3$ subunit than with the $\alpha 1$ subunit; and/or may interact more favourably with the $\alpha 5$ subunit than with the $\alpha 1$ subunit.

The compounds of the present invention are GABA_A receptor subtype ligands having a binding affinity (K_i) for the $\alpha 2$ and/or $\alpha 3$ and/or 30 $\alpha 5$ subunit, as measured in the assay described hereinbelow, of 200 nM or less, typically of 100 nM or less, and ideally of 20 nM or less. The

compounds in accordance with this invention may possess at least a 2-fold, suitably at least a 5-fold, and advantageously at least a 10-fold, selective affinity for the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit relative to the $\alpha 1$ subunit. However, compounds which are not selective in terms of their binding
 5 affinity for the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit relative to the $\alpha 1$ subunit are also encompassed within the scope of the present invention; such compounds will desirably exhibit functional selectivity in terms of zero or weak (positive or negative) efficacy at the $\alpha 1$ subunit and (i) a full or partial agonist profile at the $\alpha 2$ and/or $\alpha 3$ subunit, and/or (ii) an inverse
 10 agonist profile at the $\alpha 5$ subunit.

The present invention provides a compound of formula I, or an *N*-oxide thereof or a pharmaceutically acceptable salt thereof:



(I)

wherein

X¹ represents hydrogen, halogen, C₁₋₆ alkyl, trifluoromethyl or C₁₋₆ alkoxy;

X² represents hydrogen or halogen;

20 Z represents hydrogen, halogen, cyano, cyanomethyl, trifluoromethyl, nitro, hydroxy, C₁₋₆ alkoxy, formyl, C₂₋₆ alkoxycarbonyl, or an optionally substituted aryl, heteroaryl or heteroaryl(C₁₋₆)alkoxy group;

R¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -OSO₂CF₃, -SR^a, -SOR^a, -SO₂R^a,

-SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a, -CONR^aR^b or -CR^a=NOR^b;

R² represents hydrogen or C₂₋₆ alkoxy carbonyl; and

5 R^a and R^b independently represent hydrogen, hydrocarbon or a heterocyclic group.

The present invention also provides a compound of formula I as depicted above, or an *N*-oxide thereof or a pharmaceutically acceptable salt thereof, wherein

10 R¹ represents hydrogen, hydrocarbon, a heterocyclic group, halogen, cyano, trifluoromethyl, nitro, -OR^a, -SR^a, -SOR^a, -SO₂R^a, -SO₂NR^aR^b, -NR^aR^b, -NR^aCOR^b, -NR^aCO₂R^b, -COR^a, -CO₂R^a, -CONR^aR^b or -CR^a=NOR^b; and

X¹, X², Z, R², R^a and R^b are as defined above.

15 Where Z in the compounds of formula I above represents aryl, heteroaryl or heteroaryl(C₁₋₆)alkoxy, this group may be unsubstituted, or substituted by one or more substituents. Typically, the group Z will be unsubstituted, or substituted by one or two substituents. Typical substituents on the group Z include halogen, cyano, trifluoromethyl, nitro, C₁₋₆ alkyl, hydroxy, C₁₋₆ alkoxy, oxy, C₁₋₆ alkylsulphonyl, amino, 20 aminocarbonyl, formyl, C₂₋₆ alkoxy carbonyl and -CR^a=NOR^b, wherein R^a and R^b are as defined above. Illustrative substituents on Z include halogen, cyano, trifluoromethyl and C₁₋₆ alkyl.

For use in medicine, the salts of the compounds of formula I will be pharmaceutically acceptable salts. Other salts may, however, be useful in 25 the preparation of the compounds according to the invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable 30 acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic

acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₃₋₇ cycloalkyl(C₁₋₆)alkyl, indanyl, aryl and aryl(C₁₋₆)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C₃₋₇ heterocycloalkyl, C₃₋₇ heterocycloalkenyl, C₃₋₇ heterocycloalkyl(C₁₋₆)alkyl, heteroaryl and heteroaryl(C₁₋₆)alkyl groups.

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl, butyl and pentyl groups. Particular alkyl groups are methyl, ethyl, *n*-propyl, isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl. Derived expressions such as "C₁₋₆ alkoxy", "C₁₋₆ alkylamino" and "C₁₋₆ alkylsulphonyl" are to be construed accordingly.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl, allyl and dimethylallyl groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

5 Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl.

Typical examples of C₃₋₇ cycloalkyl(C₁₋₆)alkyl groups include cyclopropylmethyl, cyclohexylmethyl and cyclohexylethyl.

Particular indanyl groups include indan-1-yl and indan-2-yl.

10 Particular aryl groups include phenyl and naphthyl, preferably phenyl.

Particular aryl(C₁₋₆)alkyl groups include benzyl, phenylethyl, phenylpropyl and naphthylmethyl.

Suitable heterocycloalkyl groups include azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl groups.

15 A typical heterocycloalkenyl group is dihydropyrrolyl.

Suitable heteroaryl groups include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, 20 oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl groups.

The expression "heteroaryl(C₁₋₆)alkyl" as used herein includes furylmethyl, furylethyl, thienylmethyl, thienylethyl, pyrazolylmethyl, oxazolylmethyl, oxazolylethyl, thiazolylmethyl, thiazolylethyl, imidazolylmethyl, imidazolylethyl, oxadiazolylmethyl, oxadiazolylethyl, 25 thiadiazolylmethyl, thiadiazolylethyl, triazolylmethyl, triazolylethyl, tetrazolylmethyl, tetrazolylethyl, pyridinylmethyl, pyridinylethyl, pyrimidinylmethyl, pyrazinylmethyl, quinolinylmethyl and isoquinolinylmethyl.

30 The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups selected from C₁₋₆ alkyl, adamantyl, phenyl, halogen, C₁₋₆ haloalkyl, C₁₋₆ aminoalkyl, trifluoromethyl, hydroxy,

C₁₋₆ alkoxy, aryloxy, keto, C₁₋₃ alkylenedioxy, nitro, cyano, carboxy, C₂₋₆ alkoxy carbonyl, C₂₋₆ alkoxy carbonyl(C₁₋₆)alkyl, C₂₋₆ alkyl carbonyloxy, aryl carbonyloxy, aminocarbonyloxy, C₂₋₆ alkyl carbonyl, aryl carbonyl, C₁₋₆ alkylthio, C₁₋₆ alkylsulphinyl, C₁₋₆ alkylsulphonyl, arylsulphonyl, -NR^vR^w,
 5 -NR^vCOR^w, -NR^vCO₂R^w, -NR^vSO₂R^w, -CH₂NR^vSO₂R^w, -NHCONR^vR^w,
 -CONR^vR^w, -SO₂NR^vR^w and -CH₂SO₂NR^vR^w, in which R^v and R^w independently represent hydrogen, C₁₋₆ alkyl, aryl or aryl(C₁₋₆)alkyl.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluoro or chloro.

10 Where the compounds according to the invention have at least one asymmetric centre, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion
 15 are encompassed within the scope of the present invention.

Suitable values for the X¹ substituent include hydrogen, fluoro, chloro, methyl, trifluoromethyl and methoxy; in particular hydrogen or fluoro; and especially fluoro.

20 Typical values of X² include hydrogen and fluoro, especially hydrogen.

Typically, Z represents an optionally substituted aryl or heteroaryl group.

25 Selected values for the substituent Z include phenyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl and tetrazolyl, any of which groups may be optionally substituted by one or more substituents.

In one favoured embodiment, Z represents an optionally substituted phenyl group, in particular monosubstituted or disubstituted phenyl. In
 30 another favoured embodiment, Z represents optionally substituted

pyridinyl, especially unsubstituted, monosubstituted or disubstituted pyridin-2-yl, pyridin-3-yl or pyridin-4-yl.

Examples of suitable substituents on the group Z include fluoro, chloro, cyano, trifluoromethyl, nitro, methyl, hydroxy, methoxy, oxy,
5 methanesulphonyl, amino, aminocarbonyl, formyl, methoxycarbonyl and -CH=NOH.

Examples of particular substituents on the group Z include fluoro, cyano, trifluoromethyl and methyl, especially fluoro or cyano.

Detailed values of Z include cyanophenyl, (cyano)(fluoro)phenyl,
10 (chloro)(cyano)phenyl, nitrophenyl, methoxyphenyl, methanesulphonyl-phenyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, (amino)(chloro)pyridinyl, cyano-pyridinyl, methyl-pyridinyl, hydroxy-pyridinyl, methoxy-pyridinyl, oxy-pyridinyl, aminocarbonyl-pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, cyano-thienyl, aminocarbonyl-thienyl,
15 formyl-thienyl, methoxycarbonyl-thienyl, thienyl-CH=NOH, thiazolyl, isothiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl and methyl-tetrazolyl.

Specific values of Z include hydrogen, fluoro, bromo, cyano, cyanomethyl, trifluoromethyl, nitro, hydroxy, methoxy, isopropoxy, formyl,
20 methoxycarbonyl, (cyano)(fluoro)phenyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, triazolyl, (methyl)(trifluoromethyl)pyrazolyl-methoxy, methyltriazolyl-methoxy and pyridinyl-methoxy.

Suitably, R^1 represents hydrocarbon, a heterocyclic group, $-OR^a$, $-OSO_2CF_3$, $-SR^a$, $-NR^aR^b$ or $-CO_2R^a$.

25 Typically, R^1 represents hydrocarbon, a heterocyclic group, $-OR^a$, $-NR^aR^b$ or $-CO_2R^a$.

Typical values of R^a include C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-7} cycloalkyl and aryl(C_{1-6})alkyl (optionally substituted by C_{1-6} alkoxy). Suitably, R^a represents methyl, ethyl, *n*-propyl, isopropyl, allyl, cyclopropyl, cyclohexyl,
30 benzyl or methoxybenzyl. Additionally, R^a may represent *tert*-butyl.

Typical values of R^b include hydrogen and C₁₋₆ alkyl. Suitably, R^b represents hydrogen or methyl, especially hydrogen.

Favourably, R¹ represents aryl or heteroaryl, either of which groups may be substituted by one or more substituents. Typically, the aryl or heteroaryl group R¹ will be unsubstituted, or substituted by one or two substituents. Suitable substituents include halogen, C₁₋₆ alkyl, trifluoromethyl, C₁₋₆ alkoxy and cyano. Particular substituents include fluoro, chloro, methyl, trifluoromethyl, methoxy and cyano, especially fluoro.

Typical values of R¹ include phenyl, halophenyl, dihalophenyl, (C₁₋₆ alkyl)(halo)phenyl, (trifluoromethyl)(halo)phenyl, C₁₋₆ alkoxyphenyl, (C₁₋₆ alkoxy)(halo)phenyl, cyanophenyl, (cyano)(halo)phenyl, C₃₋₇ heterocycloalkenyl, heteroaryl (optionally substituted by one or more halogen atoms), C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, aryl(C₁₋₆)alkoxy, triflyloxy, C₁₋₆ alkylthio, C₁₋₆ alkylamino, C₂₋₆ alkenylamino, C₃₋₇ cycloalkylamino, aryl(C₁₋₆)alkylamino (optionally substituted by C₁₋₆ alkoxy) and C₂₋₆ alkoxycarbonyl.

Suitable values of R¹ include phenyl, halophenyl, dihalophenyl, C₁₋₆ alkoxyphenyl, cyanophenyl, (cyano)(halo)phenyl, C₃₋₇ heterocycloalkenyl, heteroaryl (optionally substituted by halo), C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, aryl(C₁₋₆)alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenylamino, C₃₋₇ cycloalkylamino, aryl(C₁₋₆)alkylamino (optionally substituted by C₁₋₆ alkoxy) and C₂₋₆ alkoxycarbonyl.

Particular values of R¹ include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, (chloro)(fluoro)phenyl, (fluoro)(methyl)phenyl, (fluoro)(trifluoromethyl)phenyl, methoxyphenyl, (fluoro)(methoxy)phenyl, cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl, methoxy, ethoxy, allyloxy, benzyloxy, triflyloxy, ethylthio, *tert*-butylthio, methylamino, ethylamino, propylamino, isopropylamino, allylamino,

cyclopropylamino, cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

Individual values of R¹ include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, methoxyphenyl, cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl, methoxy, ethoxy, allyloxy, benzyloxy, methylamino, ethylamino, propylamino, isopropylamino, allylamino, cyclopropylamino, cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

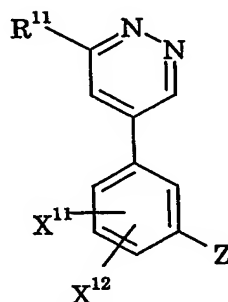
In one embodiment, R¹ represents fluorophenyl (especially 2-fluorophenyl).

In another embodiment, R¹ represents fluoro-pyridinyl (especially 3-fluoropyridin-2-yl).

In a further embodiment, R¹ represents difluoro-pyridinyl. In one aspect of this embodiment, R¹ represents 3,5-difluoropyridin-4-yl. In another aspect of this embodiment, R¹ represents 3,5-difluoropyridin-2-yl.

Suitably, R² represents hydrogen, methoxycarbonyl or ethoxycarbonyl. In a particular embodiment, R² represents hydrogen.

A particular sub-class of compounds according to the invention is represented by the compounds of formula IIA, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IIA)

wherein

Z is as defined above;

X¹¹ represents hydrogen, fluoro, chloro, methyl, trifluoromethyl or methoxy;

X¹² represents hydrogen or fluoro; and

R¹¹ represents phenyl, halophenyl, dihalophenyl, (C₁₋₆ alkyl)-
5 (halo)phenyl, (trifluoromethyl)(halo)phenyl, C₁₋₆ alkoxyphenyl, (C₁₋₆
alkoxy)(halo)phenyl, cyanophenyl, (cyano)(halo)phenyl, C₃₋₇
heterocycloalkenyl, heteroaryl (optionally substituted by one or more
halogen atoms), C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, aryl(C₁₋₆)alkoxy, triflyloxy,
C₁₋₆ alkylthio, C₁₋₆ alkylamino, C₂₋₆ alkenylamino, C₃₋₇ cycloalkylamino,
10 aryl(C₁₋₆)alkylamino (optionally substituted by C₁₋₆ alkoxy) or C₂₋₆
alkoxycarbonyl.

The present invention also provides a compound of formula IIA as depicted above, or an *N*-oxide thereof or a pharmaceutically acceptable salt thereof, wherein

15 R¹¹ represents phenyl, halophenyl, dihalophenyl, C₁₋₆ alkoxyphenyl, cyanophenyl, (cyano)(halo)phenyl, C₃₋₇ heterocycloalkenyl, heteroaryl (optionally substituted by halo), C₁₋₆ alkoxy, C₂₋₆ alkenyloxy, aryl(C₁₋₆)alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenylamino, C₃₋₇ cycloalkylamino, aryl(C₁₋₆)alkylamino (optionally substituted by C₁₋₆ alkoxy) or C₂₋₆
20 alkoxycarbonyl; and

Z, X¹¹ and X¹² are as defined above.

Suitable values of X¹¹ include hydrogen and fluoro, especially fluoro.

In a favoured embodiment, X¹² represents hydrogen. In another embodiment, X¹² represents fluoro.

25 Where R¹¹ represents heteroaryl, this group is suitably pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl or triazolyl, especially pyridinyl.

Particular values of R¹¹ include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, (chloro)(fluoro)phenyl, (fluoro)(methyl)phenyl, (fluoro)(trifluoromethyl)phenyl, methoxyphenyl, (fluoro)(methoxy)phenyl,
30 cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, difluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl,

methoxy, ethoxy, allyloxy, benzyloxy, triflyloxy, ethylthio, *tert*-butylthio, methylamino, ethylamino, propylamino, isopropylamino, allylamino, cyclopropylamino, cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

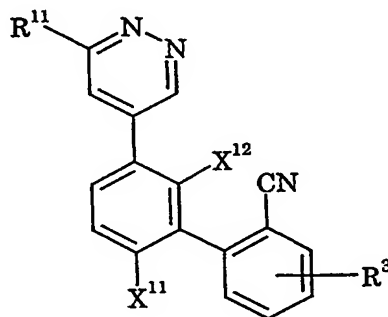
5 Individual values of R^{11} include phenyl, fluorophenyl, chlorophenyl, difluorophenyl, methoxyphenyl, cyanophenyl, (cyano)(fluoro)phenyl, dihydropyrrolyl, pyridinyl, fluoro-pyridinyl, pyrazinyl, furyl, thienyl, thiazolyl, triazolyl, methoxy, ethoxy, allyloxy, benzyloxy, methylamino, ethylamino, propylamino, isopropylamino, allylamino, cyclopropylamino, 10 cyclohexylamino, benzylamino, methoxybenzyl-amino and ethoxycarbonyl.

In one embodiment, R^{11} represents fluorophenyl (especially 2-fluorophenyl).

In another embodiment, R^{11} represents fluoro-pyridinyl (especially 3-fluoropyridin-2-yl).

15 In a further embodiment, R^{11} represents difluoro-pyridinyl. In one aspect of this embodiment, R^{11} represents 3,5-difluoropyridin-4-yl. In another aspect of this embodiment, R^{11} represents 3,5-difluoropyridin-2-yl.

One representative subset of the compounds of formula IIA above is represented by the compounds of formula IIB, and *N*-oxides thereof and 20 pharmaceutically acceptable salts thereof:



(IIB)

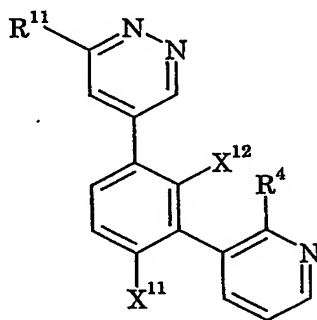
wherein X^{11} , X^{12} and R^{11} are as defined above; and

R³ represents hydrogen or fluoro.

In one embodiment, R³ is hydrogen.

In another embodiment, R³ is fluoro, in which case the fluorine atom R³ is favourably attached to the phenyl ring at the 4-, 5- or 6-position (relative to the cyano group at position 2).

Another representative subset of the compounds of formula IIA above is represented by the compounds of formula IIC, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IIC)

wherein X¹¹, X¹² and R¹¹ are as defined above; and

R⁴ represents hydrogen, fluoro, cyano or methyl.

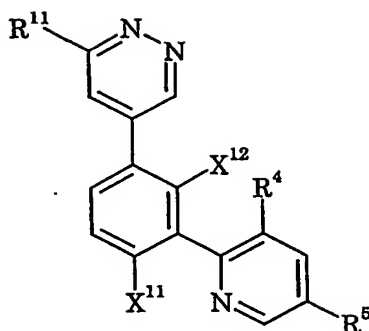
In one embodiment, R⁴ is hydrogen.

In an additional embodiment, R⁴ is fluoro.

In another embodiment, R⁴ is cyano.

In a further embodiment, R⁴ is methyl.

A further representative subset of the compounds of formula IIA above is represented by the compounds of formula IID, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:



(IID)

wherein X^{11} , X^{12} , R^4 and R^{11} are as defined above; and

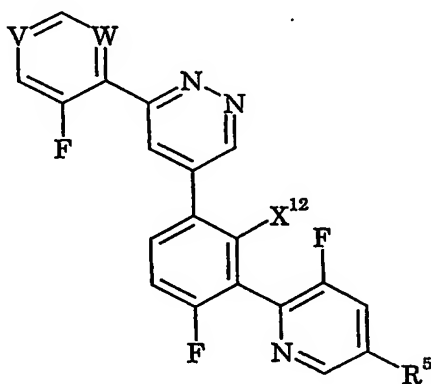
R^5 represents hydrogen or fluoro.

5 Suitably, R^5 represents hydrogen.

In another embodiment, R^5 represents fluoro.

A favoured subset of the compounds of formula IID above is represented by the compounds of formula IIE, and *N*-oxides thereof and pharmaceutically acceptable salts thereof:

10



(IIE)

wherein

V represents N and W represents CF; or

15 V represents CF and W represents N; and

X^{12} and R^5 are as defined above.

In one embodiment, V is N and W is CF.

In another embodiment, V is CF and W is N.

Specific compounds within the scope of the present invention include:

- 5 3,5-diphenylpyridazine-4-carboxylic acid ethyl ester;
- 3,5-diphenylpyridazine-4-carboxylic acid methyl ester;
- 3,5-diphenylpyridazine;
- 5-[2-fluoro-3-(pyridin-3-yl)phenyl]3-phenylpyridazine;
- 5-(3-isopropoxyphenyl)-3-phenylpyridazine;
- 10 3-(6-phenylpyridazin-4-yl)benzaldehyde;
- 4,2'-difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;
- 5-(3-cyanophenyl)-3-phenylpyridazine;
- 5-(3-bromophenyl)-3-phenylpyridazine;
- 3-phenyl-5-[3-(pyridin-3-yl)phenyl]pyridazine;
- 15 3-phenyl-5-(3-[1,2,4]triazol-4-ylphenyl)pyridazine;
- 5-[2,4-difluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;
- 5-[3-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine;
- 6,2'-difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;
- 5-[4-fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;
- 20 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-phenylpyridazine;
- 3-phenyl-5-[3-(pyridin-2-ylmethoxy)phenyl]pyridazine;
- 5-[4-fluoro-3-(3-fluoropyridin-4-yl)phenyl]-3-phenylpyridazine;
- 5-[2-fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine;
- 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-phenylpyridazine;
- 25 5-[4-fluoro-3-(pyridin-3-yl)phenyl]-3-phenylpyridazine;
- [3-(6-phenylpyridazin-4-yl)phenyl]acetonitrile;
- 2-fluoro-5-(6-phenylpyridazin-4-yl)benzonitrile;
- 5-(3-nitrophenyl)-3-phenylpyridazine;
- 3-(6-phenylpyridazin-4-yl)benzoic acid methyl ester;
- 30 3-(6-phenylpyridazin-4-yl)benzaldehyde;
- 5-(3-fluorophenyl)-3-phenylpyridazine;

- 3-phenyl-5-(3-trifluoromethylphenyl)pyridazine;
 5-(3-methoxyphenyl)-3-phenylpyridazine;
 5,2'-difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;
 3,2'-difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;
 5 5-(4-fluoro-3-methoxyphenyl)-3-phenylpyridazine;
 6,2'-difluoro-5'-[6-(4-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 4-fluoro-3'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile;
 6,2'-difluoro-5'-[6-(thien-2-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 6,2'-difluoro-5'-[6-(4-methoxyphenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 10 5'-[6-(3-chlorophenyl)pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile;
 6,2'-difluoro-5'-[6-(pyridin-3-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 5'-[6-(4-chlorophenyl)pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile;
 6,2'-difluoro-5'-[6-(pyridin-4-yl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-fluorophenyl)-
 15 pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(2-fluorophenyl)pyridazine;
 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-
 pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-3-yl)pyridazine;
 20 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluorophenyl)-
 pyridazine;
 3-(2,4-difluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-
 pyridazine;
 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-methoxyphenyl)-
 25 pyridazine;
 6,2'-difluoro-5'-[6-(2-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 6,2'-difluoro-5'-[6-(3-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 3-[6-(3-fluorophenyl)pyridazin-4-yl]benzonitrile;
 3-[6-(2-fluorophenyl)pyridazin-4-yl]benzonitrile;
 30 3-[6-(4-fluorophenyl)pyridazin-4-yl]benzonitrile;
 3-[6-(4-methoxyphenyl)pyridazin-4-yl]benzonitrile;

- 3-[6-(3,4-difluorophenyl)pyridazin-4-yl]benzonitrile;
 3-[6-(2,4-difluorophenyl)pyridazin-4-yl]benzonitrile;
 5'-[6-(2-chlorophenyl)pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile;
 3-(4-methoxyphenyl)-5-phenylpyridazine;
 5 4-fluoro-3'-[6-(4-methoxyphenyl)pyridazin-4-yl]biphenyl-2-carbonitrile;
 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-methoxyphenyl)-
 pyridazine;
 3-(4-chlorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-
 pyridazine;
 10 2-{5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazin-3-yl}-5-
 fluorobenzonitrile;
 3-(4-chlorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-3-yl)pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-2-yl)pyridazine;
 15 3-(2,3-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-
 pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thien-3-yl)pyridazine;
 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thien-2-yl)pyridazine;
 3-(2,5-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-
 20 pyridazine;
 3-(3,4-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-
 pyridazine;
 4-{5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazin-3-yl}benzonitrile;
 N-[5-(3-bromophenyl)pyridazin-3-yl]-N-methylamine;
 25 N-[5-(3-bromophenyl)pyridazin-3-yl]-N-isopropylamine;
 N-[5-(3-bromophenyl)pyridazin-3-yl]-N-cyclopropylamine;
 N-allyl-N-[5-(3-bromophenyl)pyridazin-3-yl]amine;
 N-[5-(3-bromophenyl)pyridazin-3-yl]-N-ethylamine
 N-benzyl-N-[5-(3-bromophenyl)pyridazin-3-yl]amine;
 30 N-[5-(3-bromophenyl)pyridazin-3-yl]-N-(2-methoxybenzyl)amine;
 5-(3-bromophenyl)-3-(2,5-dihydropyrrol-1-yl)pyridazine;

- 5-(3-bromophenyl)-3-ethoxypyridazine;
3-allyloxy-5-(3-bromophenyl)pyridazine;
3-(6-isopropylaminopyridazin-4-yl)benzonitrile;
3-(6-benzylaminopyridazin-4-yl)benzonitrile;
5 3-[6-(2-methoxybenzylamino)pyridazin-4-yl]benzonitrile;
3-(6-benzyloxypyridazin-4-yl)benzonitrile;
3'-(6-ethylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
4-fluoro-3'-(6-isopropylaminopyridazin-4-yl)biphenyl-2-carbonitrile;
4-fluoro-3'-(6-propylaminopyridazin-4-yl)biphenyl-2-carbonitrile;
10 3'-(6-cyclopropylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
3'-(6-allylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
3'-(6-benzylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
4-fluoro-3'-(6-methylaminopyridazin-4-yl)biphenyl-2-carbonitrile;
4-fluoro-3'-(6-methoxypyridazin-4-yl)biphenyl-2-carbonitrile;
15 3'-(6-ethoxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
3'-(6-benzyloxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile;
5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine;
5-[4-fluoro-3-(2-methyl-2*H*-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine;
20 5-[4-fluoro-3-(1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-ylmethoxy)phenyl]-3-phenylpyridazine;
5-[4-fluoro-3-(pyridin-4-ylmethoxy)phenyl]-3-phenylpyridazine;
5-[4-fluoro-3-(pyridin-3-ylmethoxy)phenyl]-3-phenylpyridazine;
5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-4-yl)pyridazine;
25 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyrazin-2-yl)pyridazine;
5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thiazol-2-yl)pyridazine;
5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-2-yl)pyridazine;
5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-4-yl)pyridazine;
30 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(1*H*-[1,2,3]triazol-4-yl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine-3-carboxylic acid
ethyl ester;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-
pyridazine-1-oxide;

5 3-(2,6-difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-
pyridazine;

3-(4-chloro-2-fluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-
fluorophenyl]pyridazine;

10 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-
trifluoromethylphenyl)pyridazine;
5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-methylphenyl)-
pyridazine;

3-(3,5-difluoropyridin-2-yl)-5-[3-(3,5-difluoropyridin-2-yl)-4-
fluorophenyl]pyridazine;

15 trifluoromethanesulfonic acid 5-[4-fluoro-3-(3-fluoropyridin-2-
yl)phenyl]pyridazin-3-yl ester;

3-ethylsulfanyl-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;

3-*tert*-butylsulfanyl-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;

20 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluoropyridin-4-yl)-
pyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluoropyridin-2-yl)-
pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-2-yl)-
pyridazine;

25 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-4-yl)-
pyridazine 1-oxide;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoro-1-oxypyridin-4-yl)-
pyridazine;

30 5-[2,4-difluoro-3-(3,5-difluoropyridin-2-yl)phenyl]-3-(3,5-difluoropyridin-4-
yl)pyridazine;

5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-methoxyphenyl)pyridazine;

5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(2-fluoro-4-methoxyphenyl)-pyridazine;

5 3-(3,5-difluoropyridin-4-yl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;

3-(3,5-difluoropyridin-2-yl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine;

10 3-(3,5-difluoropyridin-4-yl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine;

and pharmaceutically acceptable salts thereof.

Also provided by the present invention is a method for the treatment and/or prevention of anxiety which comprises administering to a patient in need of such treatment an effective amount of a compound of
15 formula I as defined above or a pharmaceutically acceptable salt thereof.

Further provided by the present invention is a method for the treatment and/or prevention of convulsions (e.g. in a patient suffering from epilepsy or a related disorder) which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I
20 as defined above or a pharmaceutically acceptable salt thereof.

The binding affinity (K_i) of the compounds according to the present invention for the $\alpha 3$ subunit of the human GABA_A receptor is conveniently as measured in the assay described hereinbelow. The $\alpha 3$ subunit binding
25 affinity (K_i) of the anxiolytic compounds of the invention is ideally 50 nM or less, preferably 10 nM or less, and more preferably 5 nM or less.

The anxiolytic compounds according to the present invention will ideally elicit at least a 40%, preferably at least a 50%, and more preferably at least a 60%, potentiation of the GABA EC₂₀ response in stably
transfected recombinant cell lines expressing the $\alpha 3$ subunit of the human
30 GABA_A receptor. Moreover, the compounds of the invention will ideally elicit at most a 30%, preferably at most a 20%, and more preferably at

most a 10%, potentiation of the GABA EC₂₀ response in stably transfected recombinant cell lines expressing the α 1 subunit of the human GABA_A receptor.

5 The potentiation of the GABA EC₂₀ response in stably transfected cell lines expressing the α 3 and α 1 subunits of the human GABA_A receptor can conveniently be measured by procedures analogous to the protocol described in Wafford *et al.*, *Mol. Pharmacol.*, 1996, 50, 670-678. The procedure will suitably be carried out utilising cultures of stably transfected eukaryotic cells, typically of stably transfected mouse Ltk-
10 fibroblast cells.

 The compounds according to the present invention may exhibit anxiolytic activity, as may be demonstrated by a positive response in the elevated plus maze and conditioned suppression of drinking tests (cf. Dawson *et al.*, *Psychopharmacology*, 1995, 121, 109-117). Moreover, the
15 compounds of the invention are likely to be substantially non-sedating, as may be confirmed by an appropriate result obtained from the response sensitivity (chain-pulling) test (cf. Bayley *et al.*, *J. Psychopharmacol.*, 1996, 10, 206-213).

 The compounds according to the present invention may also exhibit
20 anticonvulsant activity. This can be demonstrated by the ability to block pentylenetetrazole-induced seizures in rats and mice, following a protocol analogous to that described by Bristow *et al.* in *J. Pharmacol. Exp. Ther.*, 1996, 279, 492-501.

 In another aspect, the present invention provides a method for the
25 treatment and/or prevention of cognitive disorders, including dementing conditions such as Alzheimer's disease, which comprises administering to a patient in need of such treatment an effective amount of a compound of formula I as defined above or a pharmaceutically acceptable salt thereof.

 Cognition enhancement can be shown by testing the compounds in
30 the Morris watermaze as reported by McNamara and Skelton,

Psychobiology, 1993, 21, 101-108. Further details of relevant methodology are described in WO 96/25948.

Cognitive disorders for which the compounds of the present invention may be of benefit include delirium, dementia, amnesic disorders, and cognition deficits, including age-related memory deficits, due to traumatic injury, stroke, Parkinson's disease and Down Syndrome. Any of these conditions may be attributable to substance abuse or withdrawal. Examples of dementia include dementia of the Alzheimer's type with early or late onset, and vascular dementia, any of which may be uncomplicated or accompanied by delirium, delusions or depressed mood; and dementia due to HIV disease, head trauma, Parkinson's disease or Creutzfeld-Jakob disease.

In order to elicit their behavioural effects, the compounds of the invention will ideally be brain-penetrant; in other words, these compounds will be capable of crossing the so-called "blood-brain barrier". Preferably, the compounds of the invention will be capable of exerting their beneficial therapeutic action following administration by the oral route.

The invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a

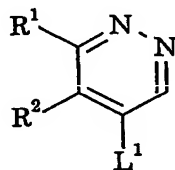
pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

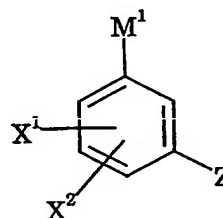
In the treatment of neurological disorders, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per

day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The compounds in accordance with the present invention may be prepared by a process which comprises reacting a compound of formula III
5 with a compound of formula IV:



(III)



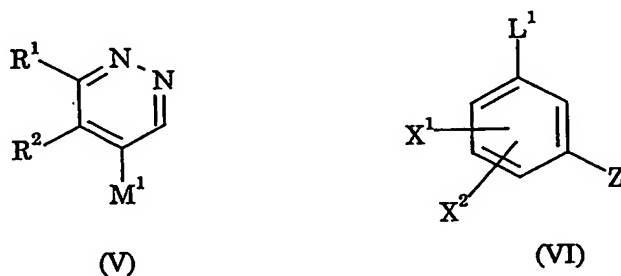
(IV)

wherein X¹, X², Z, R¹ and R² are as defined above, L¹ represents a suitable
10 leaving group, and M¹ represents a boronic acid moiety -B(OH)₂ or a cyclic ester thereof formed with an organic diol, e.g. pinacol, 1,3-propanediol or neopentyl glycol, or M¹ represents -Sn(Alk)₃ in which Alk represents a C₁-₆ alkyl group, typically *n*-butyl; in the presence of a transition metal catalyst.

15 The leaving group L¹ is typically a halogen atom, e.g. iodo, bromo or chloro.

The transition metal catalyst of use in the reaction between compounds III and IV is suitably tetrakis(triphenylphosphine)-palladium(0). The reaction is conveniently carried out at an elevated
20 temperature in a solvent such as *N,N*-dimethylacetamide, 1,4-dioxane or tetrahydrofuran, advantageously in the presence of potassium phosphate, copper(I) iodide, sodium carbonate or cesium carbonate. Alternatively, the transition metal catalyst employed may be dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II), in which case the reaction is
25 conveniently effected at an elevated temperature in a solvent such as *N,N*-dimethylformamide, advantageously in the presence of potassium phosphate.

In an alternative procedure, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula V with a compound of formula VI:

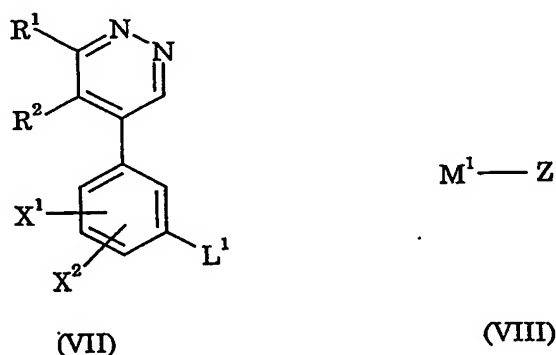


5

wherein X¹, X², Z, R¹, R², L¹ and M¹ are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

10

In another procedure, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula VII with a compound of formula VIII:



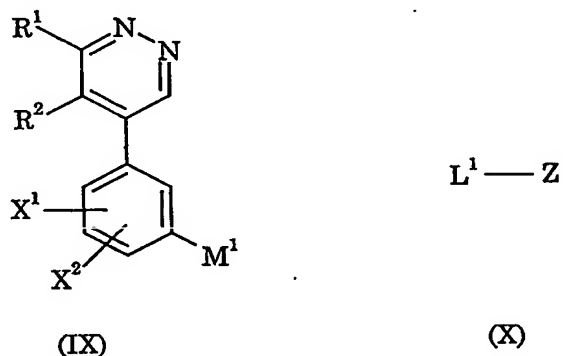
15

wherein X¹, X², Z, R¹, R², L¹ and M¹ are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In the compounds of formula VI and VII above, the leaving group L¹ is typically trifluoromethanesulfonyloxy (triflyloxy); or a halogen atom, e.g. bromo.

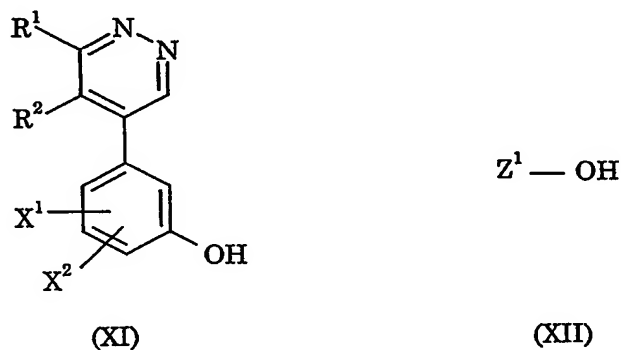
20

Alternatively, the compounds according to the present invention may be prepared by a process which comprises reacting a compound of formula IX with a compound of formula X:



wherein X¹, X², Z, R¹, R², L¹ and M¹ are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

In an additional procedure, the compounds according to the present invention in which Z represents C₁₋₆ alkoxy or optionally substituted heteroaryl(C₁₋₆)alkoxy may be prepared by a process which comprises reacting a compound of formula XI with a compound of formula XII:



wherein X¹, X², R¹ and R² are as defined above, and Z¹ represents C₁₋₆ alkyl or optionally substituted heteroaryl(C₁₋₆)alkyl; in the presence of triphenylphosphine and a dialkyl azodicarboxylate, e.g. diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD).

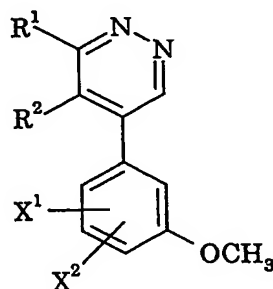
The reaction is conveniently carried out by stirring in a solvent such as tetrahydrofuran.

Where M^1 in the intermediates of formula IV and IX above represents a boronic acid moiety $-B(OH)_2$ or a cyclic ester thereof formed with pinacol or neopentyl glycol, the relevant compound IV or IX may be prepared by reacting bis(pinacolato)diboron or bis(neopentyl glycolato)diborane respectively with a compound of formula VI or VII as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the reaction between bis(pinacolato)diboron or bis(neopentyl glycolato)diborane and compound VI or VII is suitably dichloro[1,1'-bis(diphenylphosphino)ferrocene]-palladium(II). The reaction is conveniently carried out at an elevated temperature in a solvent such as 1,4-dioxane, optionally in admixture with dimethylsulfoxide, typically in the presence of 1,1'-bis(diphenylphosphino)ferrocene and/or potassium acetate.

Where L^1 in the intermediates of formula VII above represents triflyloxy, the relevant compound VII may be prepared by reacting the appropriate compound of formula XI as defined above with triflic anhydride, typically in the presence of pyridine. Analogous conditions may be utilised for preparing a compound of formula VI wherein L^1 represents triflyloxy from the corresponding hydroxy precursor.

The intermediates of formula XI above may suitably be prepared from the appropriate methoxy-substituted precursor of formula XIII:

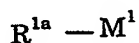


(XIII)

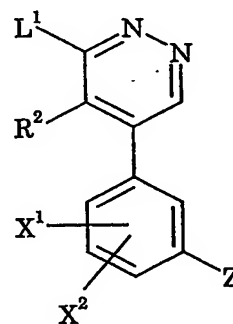
wherein X^1 , X^2 , R^1 and R^2 are as defined above; by treatment with boron tribromide, typically in chloroform or dichloromethane; or with hydrogen bromide, typically in acetic acid at reflux.

5 Where M^1 in the intermediates of formula V above represents $-\text{Sn}(\text{Alk})_3$ and Alk is as defined above, this compound may be prepared by reacting a compound of formula III as defined above with a reagent of formula $(\text{Alk})_3\text{Sn-Hal}$, in which Hal represents a halogen atom, typically chloro. The reaction is conveniently effected by treating compound III
10 with isopropylmagnesium chloride, typically in a solvent such as tetrahydrofuran, with subsequent addition of the stannyl reagent $(\text{Alk})_3\text{Sn-Hal}$.

In a further procedure, the compounds according to the present invention wherein R^1 represents an aryl or heteroaryl moiety may be
15 prepared by a process which comprises reacting a compound of formula XIV with a compound of formula XV:



(XIV)



(XV)

20 wherein X^1 , X^2 , Z , R^2 , L^1 and M^1 are as defined above, and R^{1a} represents an aryl or heteroaryl moiety; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

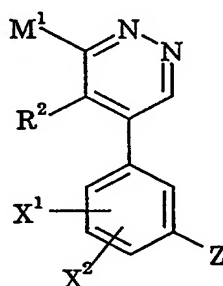
25 In the compounds of formula XV above, the leaving group L^1 is typically triflyloxy; or a halogen atom, e.g. chloro.

The transition metal catalyst of use in the reaction between compounds XIV and XV is suitably tetrakis(triphenylphosphine)-palladium(0), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as tetrahydrofuran or 1,4-dioxane, typically in the presence of sodium carbonate. Alternatively, the transition metal catalyst may suitably be palladium bis(diphenylphosphinylbutane)dichloride, in which case the reaction is conveniently effected at an elevated temperature in a solvent such as tetrahydrofuran, typically in the presence of sodium carbonate.

In a still further procedure, the compounds according to the present invention wherein R^1 represents an aryl or heteroaryl moiety may be prepared by a process which comprises reacting a compound of formula XVI with a compound of formula XVII:



(XVI)



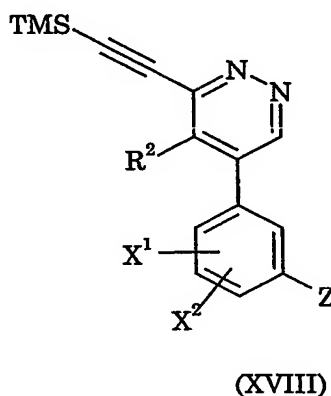
(XVII)

wherein X^1 , X^2 , Z , R^{1a} , R^2 , L^1 and M^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

The intermediates of formula XVII wherein M^1 represents $-\text{Sn}(\text{Alk})_3$ and Alk represents C_{1-6} alkyl, e.g. methyl, may be prepared by reacting a compound of formula XV as defined above with a reagent of formula $(\text{Alk})_3\text{Sn}-\text{Sn}(\text{Alk})_3$. The reaction is conveniently effected in the presence of a transition metal catalyst, e.g. tetrakis(triphenylphosphine)palladium(0),

with heating in a solvent such as 1,4-dioxane, typically in the presence of lithium chloride.

In a yet further procedure, the compounds according to the present invention wherein R¹ represents 1*H*-[1,2,3]triazol-4-yl may be prepared by
5 a process which comprises reacting a compound of formula XVIII:



wherein X¹, X², Z and R² are as defined above, and TMS is an abbreviation
10 for trimethylsilanyl; with sodium azide.

The reaction is conveniently effected by stirring the reactants in a solvent such as *N,N*-dimethylformamide.

The intermediates of formula XVIII may be prepared by reacting a compound of formula XV with TMS-acetylene, in the presence of a
15 transition metal catalyst such as bis(triphenylphosphine)palladium(II) chloride. The reaction is conveniently effected by stirring in a solvent such as tetrahydrofuran, typically in the presence of triethylamine, triphenylphosphine and copper(I) chloride.

The compounds according to the present invention wherein R¹
20 represents -OR^a may be prepared by a process which comprises reacting a compound of formula XV as defined above with a compound of formula R^a-OH, wherein R^a is as defined above. The reaction is conveniently carried out in the presence of a base such as sodium hydride or sodium ethoxide.

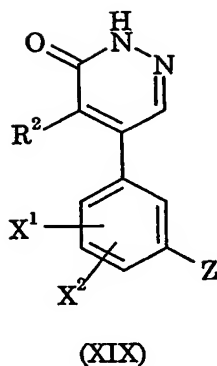
The compounds according to the present invention wherein R^1 represents $-SR^a$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with a salt of formula $R^aS\cdot Na^+$, wherein R^a is as defined above. The reaction is conveniently carried out in the presence of a solvent such as *N,N*-dimethylformamide.

The compounds according to the present invention wherein R^1 represents $-NR^aR^b$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with a compound of formula $H\cdot NR^aR^b$, wherein R^a and R^b are as defined above. The reaction is conveniently effected by stirring at an elevated temperature, typically in a solvent such as tetrahydrofuran.

The compounds according to the present invention wherein R^1 represents $-CO_2R^a$ may be prepared by a process which comprises reacting a compound of formula XV as defined above with carbon dioxide and a compound of formula $R^a\cdot OH$, wherein R^a is as defined above; in the presence of a transition metal catalyst.

The transition metal catalyst of use in the foregoing reaction is ideally [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride, in which case the reaction is conveniently carried out at an elevated temperature in a solvent such as *N,N*-dimethylformamide, optionally in admixture with dichloromethane, typically in the presence of sodium acetate.

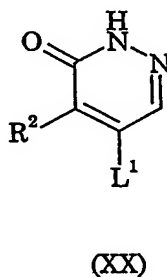
The intermediates of formula XV wherein L^1 represents triflyloxy may be prepared by reacting a compound of formula XIX:



wherein X^1 , X^2 , Z and R^2 are as defined above; with *N*-phenyltriflylimide, typically in the presence of triethylamine, in a solvent such as dichloromethane; or with triflic anhydride, typically in the presence of pyridine.

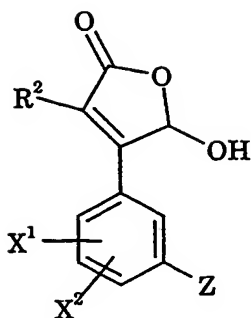
Moreover, the intermediates of formula XV wherein L^1 represents chloro may be prepared by treating the requisite compound of formula XIX with phosphorus oxychloride at an elevated temperature.

The intermediates of formula XIX may be prepared by reacting a compound of formula IV as defined above with a compound of formula XX:



wherein R^2 and L^1 are as defined above; in the presence of a transition metal catalyst; under conditions analogous to those described above for the reaction between compounds III and IV.

Alternatively, the intermediates of formula XIX may be prepared by reacting a compound of formula XXI:



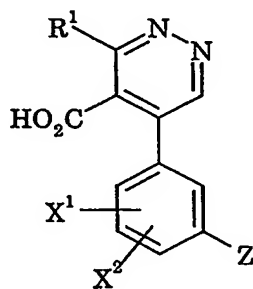
(XXI)

wherein X¹, X², Z and R² are as defined above; with hydrazine hydrate, typically in ethanol at reflux.

5 The compounds according to the present invention wherein Z represents cyano may be prepared by a process which comprises reacting a compound of formula VII above wherein L¹ represents a halogen atom, e.g. bromo, with zinc cyanide; in the presence of a transition metal catalyst.

10 The transition metal catalyst of use in the foregoing reaction is ideally tetrakis(triphenylphosphine)palladium(0), in which case the reaction is conveniently effected at an elevated temperature in a solvent such as *N,N*-dimethylformamide.

15 The compounds according to the present invention wherein R² represents methoxycarbonyl may be prepared by a process which comprises reacting a compound of formula XXII:



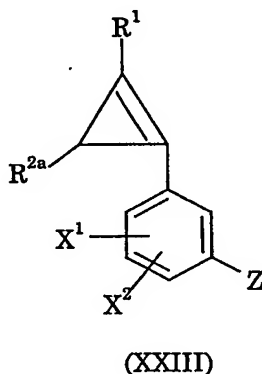
(XXII)

wherein X¹, X², Z and R¹ are as defined above; with diazomethane.

The reaction is conveniently accomplished by stirring in a solvent such as diethyl ether.

The intermediates of formula XXII may be prepared by saponifying a compound of formula I wherein R^2 represents C_{2-6} alkoxy carbonyl, typically by treatment with potassium hydroxide in refluxing aqueous methanol.

The compounds according to the present invention wherein R^2 represents C_{2-6} alkoxy carbonyl may be prepared by a process which comprises reacting a compound of formula XXIII:



wherein X^1 , X^2 , Z and R^1 are as defined above, and R^{2a} represents C_{2-6} alkoxy carbonyl; with diazomethane.

The reaction is conveniently effected by stirring in a solvent such as diethyl ether.

The compounds of formula XI and XIII above correspond to compounds of formula I as defined above wherein Z represents hydroxy and methoxy respectively, and they may therefore be prepared by any of the methods described above for the preparation of the compounds according to the invention. Moreover, where L^1 in compounds VII and XV above represents a halogen atom, or where L^1 in compound XV represents triflyloxy, these compounds correspond to compounds of formula I as defined above, and they therefore constitute compounds in accordance with the invention in their own right.

Where they are not commercially available, the starting materials of formula III, VIII, X, XII, XIV, XVI, XX, XXI and XXIII may be prepared by methods analogous to those described in the accompanying Examples, or by standard methods well known from the art.

5 It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by techniques known from the art. For example, a compound of formula I initially obtained may be converted into the *N*-oxide derivative thereof by
10 treatment with *m*-chloroperbenzoic acid. A compound of formula I wherein R^1 represents $-C(O-Alk^1)_2R^a$ initially obtained, wherein Alk^1 is C_{1-6} alkyl, typically methyl or ethyl, may be converted into the corresponding compound of formula I wherein R^1 represents $-COR^a$ by hydrolysis with a mineral acid, typically aqueous hydrochloric acid. A
15 compound wherein R^1 represents formyl may be reduced with sodium triacetoxyborohydride to the corresponding compound wherein R^1 represents hydroxymethyl. A compound of formula I wherein R^1 represents C_{2-6} alkoxycarbonyl may be reduced with lithium aluminium hydride to the corresponding compound of formula I wherein R^1 represents
20 hydroxymethyl. A compound of formula I wherein R^1 represents hydroxymethyl may be oxidised to the corresponding compound of formula I wherein R^1 represents formyl by treatment with manganese dioxide. The formyl derivative thereby obtained may be condensed with a hydroxylamine derivative of formula H_2N-OR^b to provide a compound of
25 formula I wherein R^1 represents $-CH=NOR^b$. Furthermore, a compound of formula I wherein R^1 represents $-CH=NOH$ may be treated with triethylamine in the presence of 1,1'-carbonyldiimidazole to afford a corresponding compound of formula I wherein R^1 represents cyano. Alternatively, the compound of formula I wherein R^1 represents formyl
30 may be reacted with a Grignard reagent of formula R^aMgBr to afford a compound of formula I wherein R^1 represents $-CH(OH)R^a$, and this

compound may in turn be oxidised using manganese dioxide to the corresponding compound of formula I wherein R^1 represents $-COR^a$. The latter compound may then be condensed with a hydroxylamine derivative of formula H_2N-OR^b to provide a compound of formula I wherein R^1 represents $-CR^a=NOR^b$. A compound of formula I wherein R^1 represents $-CH(OH)R^a$ may be converted into the corresponding compound of formula I wherein R^1 represents $-CHFR^a$ by treatment with (diethylamino)sulfur trifluoride (DAST). Similarly, a compound of formula I wherein R^1 represents $-COR^a$ may be converted into the corresponding compound of formula I wherein R^1 represents $-CF_2R^a$ by treatment with DAST. A compound of formula I wherein R^1 represents amino may be converted into the corresponding compound of formula I wherein R^1 represents chloro by diazotisation, using sodium nitrite, followed by treatment with copper(I) chloride. A compound of formula I wherein R^1 represents $-COCH_3$ may be treated with thioacetamide in the presence of pyridinium tribromide to furnish the corresponding compound of formula I wherein R^1 represents 2-methylthiazol-5-yl. Moreover, a compound of formula I wherein R^1 is formyl may be treated with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) in the presence of potassium carbonate to afford the corresponding compound of formula I wherein R^1 represents oxazol-5-yl. A compound of formula I wherein R^1 represents hydroxymethyl may be treated with carbon tetrabromide and triphenylphosphine to afford the corresponding compound of formula I wherein R^1 represents bromomethyl, which may then be reacted (typically *in situ*) with the sodium salt of imidazole or 1*H*-[1,2,4]triazole to provide a compound of formula I wherein R^1 represents imidazol-1-ylmethyl or [1,2,4]triazol-1-ylmethyl respectively; or with the sodium salt of 1*H*-[1,2,3]triazole to provide a mixture of compounds of formula I wherein R^1 represents [1,2,3]triazol-1-ylmethyl and [1,2,3]triazol-2-ylmethyl; or with morpholine to provide a compound of formula I wherein R^1 represents morpholin-4-ylmethyl. A compound of formula I wherein Z is substituted with methoxy may be converted to the

corresponding compound wherein Z is substituted with hydroxy by treatment with boron tribromide.

Where a mixture of products is obtained from any of the processes described above for the preparation of compounds according to the invention, the desired product can be separated therefrom at an appropriate stage by conventional methods such as preparative HPLC; or column chromatography utilising, for example, silica and/or alumina in conjunction with an appropriate solvent system.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as (-)-di-*p*-toluoyl-d-tartaric acid and/or (+)-di-*p*-toluoyl-l-tartaric acid, followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 3rd edition, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The following Examples illustrate the preparation of compounds according to the invention.

5 The compounds in accordance with this invention potently inhibit the binding of [³H]-flumazenil to the benzodiazepine binding site of human GABA_A receptors containing the $\alpha 2$ and/or $\alpha 3$ and/or $\alpha 5$ subunit stably expressed in Ltk⁻ cells.

Reagents

- Phosphate buffered saline (PBS).
- 10 • Assay buffer: 10 mM KH₂PO₄, 100 mM KCl, pH 7.4 at room temperature.
- [³H]-Flumazenil (18 nM for $\alpha 1\beta 3\gamma 2$ cells; 18 nM for $\alpha 2\beta 3\gamma 2$ cells; 10 nM for $\alpha 3\beta 3\gamma 2$ cells; 10 nM for $\alpha 5\beta 3\gamma 2$ cells) in assay buffer.
- Flunitrazepam 100 μ M in assay buffer.
- Cells resuspended in assay buffer (1 tray to 10 ml).

15

Harvesting Cells

Supernatant is removed from cells. PBS (approximately 20 ml) is added. The cells are scraped and placed in a 50 ml centrifuge tube. The procedure is repeated with a further 10 ml of PBS to ensure that most of
20 the cells are removed. The cells are pelleted by centrifuging for 20 min at 3000 rpm in a benchtop centrifuge, and then frozen if desired. The pellets are resuspended in 10 ml of buffer per tray (25 cm x 25 cm) of cells.

Assay

25 Can be carried out in deep 96-well plates or in tubes. Each tube contains:

- 300 μ l of assay buffer.
- 50 μ l of [³H]-flumazenil (final concentration for $\alpha 1\beta 3\gamma 2$: 1.8 nM; for $\alpha 2\beta 3\gamma 2$: 1.8 nM; for $\alpha 3\beta 3\gamma 2$: 1.0 nM; for $\alpha 5\beta 3\gamma 2$: 1.0 nM).

- Assays are incubated for 1 hour at 40°C, then filtered using either a Tomtec or Brandel cell harvester onto GF/B filters followed by 3 x 3 ml washes with ice cold assay buffer. Filters are dried and counted by liquid scintillation counting. Expected values for total binding are 3000-4000 dpm for total counts and less than 200 dpm for non-specific binding if using liquid scintillation counting, or 1500-2000 dpm for total counts and less than 200 dpm for non-specific binding if counting with meltilex solid scintillant. Binding parameters are determined by non-linear least squares regression analysis, from which the inhibition constant K_i can be calculated for each test compound.

20

EXAMPLE 1

3,5-Diphenylpyridazine-4-carboxylic acid ethyl ester

2,3-Diphenylcycloprop-2-enecarboxylic acid ethyl ester (3.5 g, 13.2 mmol) in diethyl ether (20 ml) was added to a solution of diazomethane (66.4 mmol) in 125 ml ether and stirred in the absence of light for 3 days. Acetic acid was added dropwise until evolution of N₂ gas had ceased. Further portions of acetic acid were added before heating to reflux for 4 h. The reaction was concentrated and purified by column chromatography using 10-30% ethyl acetate/hexanes to give the *title compound* as a pale yellow solid (1.77 g). δ_{H} (400 MHz, d⁶ DMSO) 0.84 (3H, t, *J* 7.0), 4.02 (2H, q, *J* 7.0), 7.54-7.58 (8H, m), 7.62-7.65 (2H, m), 9.48 (1H, s); *m/z* (ES⁺) 305.

EXAMPLE 2

3,5-Diphenylpyridazine-4-carboxylic acid methyl ester

5 The product from Example 1 (1.17 g, 3.84 mmol) and potassium hydroxide (0.86 g, 15.3 mmol) were heated to reflux in methanol/H₂O (25 ml/3 ml) for 18 h. The reaction was cooled to room temperature and acidified with 2N HCl to give 3,5-diphenylpyridazine-4-carboxylic acid as a pale yellow solid which was collected by filtration (0.94 g). δ_{H} (400 MHz, d⁶ DMSO) 7.55-7.57 (6H, m), 7.60-7.63 (2H, m), 7.71-7.73 (2H, m), 9.40 (1H, s); m/z (ES⁺) 277.

10 A solution of diazomethane (0.6 mmol) in diethyl ether (5 ml) was added dropwise to the product from above (0.1 g, 0.36 mmol) suspended in diethyl ether (10 ml). The resultant clear solution was stirred for 18 h. Acetic acid was added and the reaction stirred for 1 h before concentrating. The *title compound* was obtained as a pale yellow solid by recrystallising from ethyl acetate-hexanes (78 mg). δ_{H} (400 MHz, d⁶ DMSO) 3.54 (3H, s), 7.53-7.58 (8H, m), 7.62-7.66 (2H, m), 9.49 (1H, s); m/z (ES⁺) 291.

20

EXAMPLE 3

3,5-Diphenylpyridazine

25 3-Phenyl-5-(tri-*n*-butylstannyl)pyridazine (100 mg, 0.22 mmol), bromobenzene (32 μ l, 0.27 mmol) and tetrakis(triphenylphosphine)-palladium(0) (5 mg) in tetrahydrofuran (2 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor (Personal Chemistry, Uppsala, Sweden). The reaction was diluted with CH₂Cl₂ (6 ml) and H₂O (2 ml) then poured into a PTFE (5 μ M) fritted syringe barrel. The organic phase was collected and concentrated to leave 100 mg of crude product. Part of the sample was purified by HPLC with mass triggered fraction collection to give the *title compound* as a gum (3.1 mg). δ_{H} (400

30

MHz, d⁶ DMSO) 7.55-7.64 (6H, m), 8.06 (2H, dd, *J* 8.0, 1.6), 8.28 (2H, dd, *J* 8.0, 1.6), 8.46-8.47 (1H, d, *J* 4.0), 9.62 (1H, d, *J* 4.0); *m/z* (ES⁺) 233 (MH⁺).

EXAMPLE 4

5

5-[2-Fluoro-3-(pyridin-3-yl)phenyl]3-phenylpyridazine

5-Iodo-3-phenylpyridazine (60 mg, 0.14 mmol), 2-fluoro-3-(pyridin-3-yl)phenylboronic acid (32 mg), tetrakis(triphenylphosphine)palladium(0) (5 mg) and 2N Na₂CO₃ (1 ml) in tetrahydrofuran (4 ml) were combined and
 10 heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH₂Cl₂ (6 ml) and H₂O (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was collected, concentrated and recrystallised from methanol-CH₂Cl₂-isopropanol to give the *title compound* as a colourless solid (36 mg). δ_H (400 MHz, d⁶ DMSO)
 15 7.55-7.66 (5H, m), 7.77-7.81 (1H, m), 7.91-7.95 (1H, m), 8.08-8.11 (1H, m), 8.25-8.27 (2H, m), 8.48 (1H, m), 8.66 (1H, dd, *J* 1.6, 4.7), 8.87 (1H, d, *J* 2.0), 9.53 (1H, t, *J* 2.2); *m/z* (ES⁺) 328 (MH⁺).

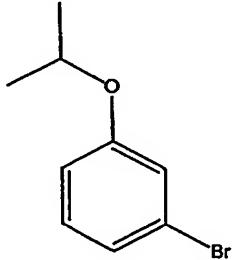
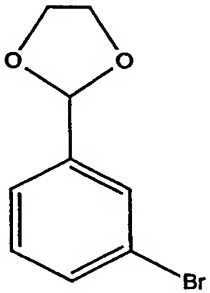
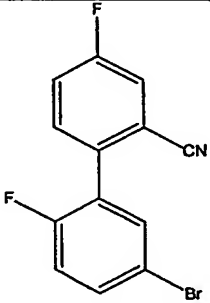
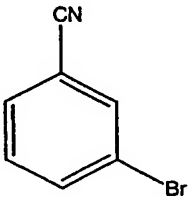
EXAMPLES 5 TO 32

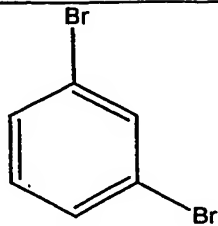
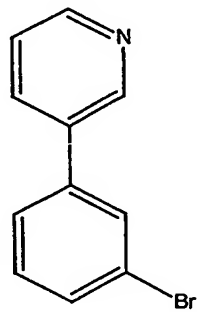
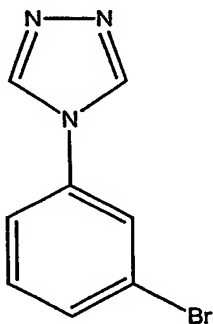
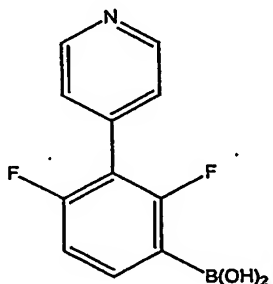
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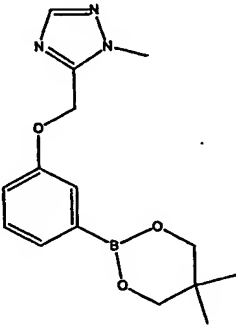
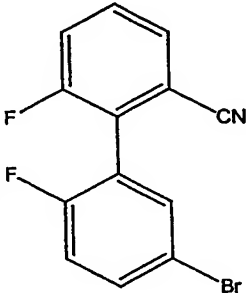
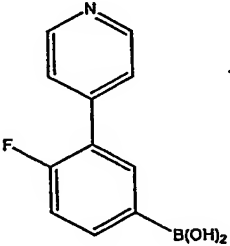
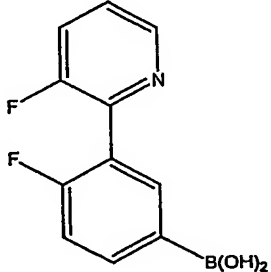
The compounds in Table 1 were prepared, using the aryl halide, boronic acid or ester starting materials shown, in an analogous manner to that described in Example 3 or 4. Samples were purified as described in Example 3 or by recrystallisation from methanol-ethyl acetate, CH₂Cl₂ or
 25 CH₂Cl₂-isopropanol.

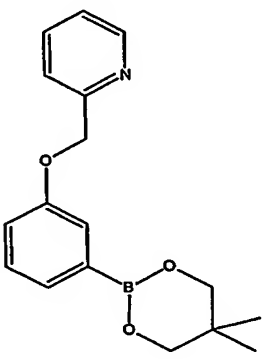
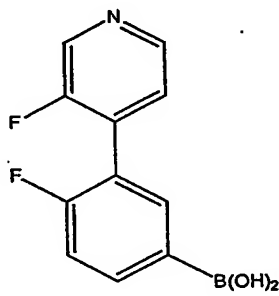
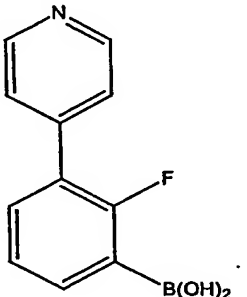
Table 1

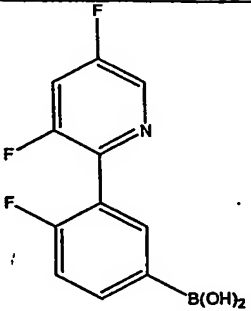
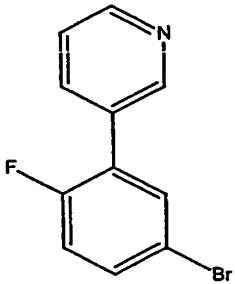
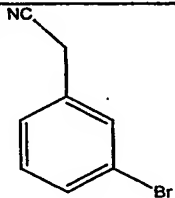
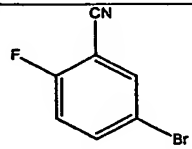
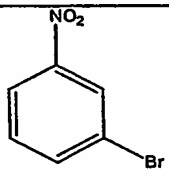
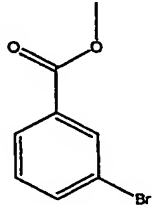
EX. NO.	STARTING MATERIAL	PRODUCT	δ _H (400 MHz, d ⁶ DMSO)	<i>m/z</i> (ES ⁺)
5		5-(3-	1.32 (6H, d, <i>J</i> 8), 4.80	291

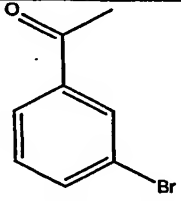
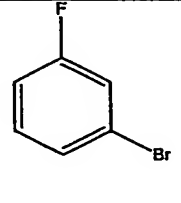
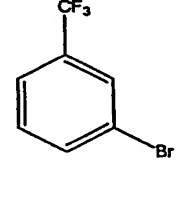
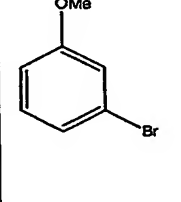
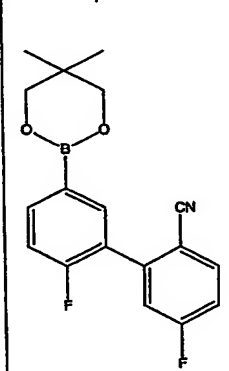
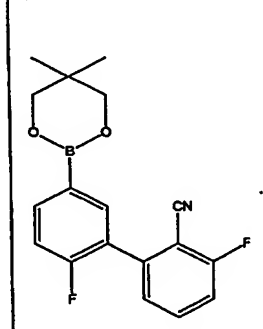
		Isopropoxy-phenyl)-3-phenyl-pyridazine	(1H, quin, <i>J</i> 8), 7.10-7.12 (1H, m), 7.48-7.61 (7H, m), 8.26-8.28 (1H, m), 8.43 (1H, d, <i>J</i> 2), 9.58 (1H, d, <i>J</i> 2).	
6		3-(6-Phenyl-pyridazin-4-yl)-benzaldehyde	7.56-7.69 (4H, m), 7.77 (1H, d, <i>J</i> 8), 7.84 (1H, d, <i>J</i> 8), 8.09 (1H, dd, <i>J</i> 1.2, 8), 8.23 (2H, m), 8.32 (1H, d, <i>J</i> 2), 9.29 (1H, d, <i>J</i> 2), 10.00 (1H, s).	261
7		4,2'-Difluoro-5'-(6-phenyl-pyridazin-4-yl)biphenyl-2-carbonitrile	7.56-7.67 (4H, m), 7.79-7.86 (2H, m), 8.05-8.08 (1H, m), 8.26-8.32 (4H, m), 8.55 (1H, d, <i>J</i> 4), 9.69 (1H, d, <i>J</i> 4)	370
8		5-(3-Cyanophenyl)-3-phenyl-pyridazine	7.57-7.64 (3H, m), 7.81 (1H, t, <i>J</i> 8), 8.03 (1H, d, <i>J</i> 8), 8.30-8.35 (2H, m), 8.41 (1H, d, <i>J</i> 8), 8.59 (1H, d, <i>J</i> 4), 8.63 (1H, s), 9.69 (1H, d, <i>J</i> 4).	258
9		5-(3-Bromophenyl)-3-phenyl-pyridazine	7.53-7.62 (4H, m), 7.76 (1H, d, <i>J</i> 12), 8.06 (1H, d, <i>J</i> 12), 8.28-8.33 (3H, m),	312

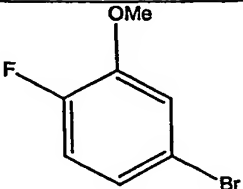
			8.51 (1H, d, <i>J</i> 4), 9.62 (1H, d, <i>J</i> 4).	
10		3-Phenyl-5-[3-(pyridin-3-yl)phenyl]pyridazine	7.48-7.66 (4H, m), 7.73 (1H, t, <i>J</i> 7.8), 7.92-7.94 (1H, m), 8.12-8.13 (1H, m), 8.26-8.33 (3H, m), 8.41 (1H, t, <i>J</i> 1.8), 8.62-8.64 (2H, m), 9.10 (1H, dd, <i>J</i> 2.0, 0.8), 9.75 (1H, d, <i>J</i> 2.3).	310
11		3-Phenyl-5-(3-[1,2,4]triazol-4-ylphenyl)pyridazine	7.56-7.66 (4H, m), 7.79 (1H, t, <i>J</i> 7.8), 7.90-7.93 (1H, m), 8.14-8.16 (1H, m), 8.29-8.31 (1H, dd, <i>J</i> 0.8, 0.8), 8.42 (1H, t, <i>J</i> 2.0), 8.61 (1H, d, <i>J</i> 2.0), 9.29 (2H, s), 9.76 (1H, d, <i>J</i> 2.3).	300
12		5-[2,4-Difluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine	7.53-7.64 (6H, m), 8.04-8.10 (1H, m), 8.26 (2H, dd, <i>J</i> 1.8, 8.0), 8.46 (1H, d, <i>J</i> 0.8), 8.77 (2H, dd, <i>J</i> 1.4, 4.5), 9.50 (1H, t, <i>J</i> 1.8).	346

13		5-[3-(2-Methyl-2H-[1,2,4]triazol-3-ylmethoxy)-phenyl]-3-phenylpyridazine	3.94 (3H, s), 5.46 (2H, s), 7.25 (1H, dd, <i>J</i> 2.0, 7.6), 7.52-7.62 (4H, m), 7.70 (1H, d, <i>J</i> 8.4), 7.79-7.80 (1H, m), 7.96 (1H, s), 8.28-8.30 (2H, m), 8.48 (1H, d, <i>J</i> 4.0), 9.63 (1H, s).	344
14		6,2'-Difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile	7.54-7.87 (6H, m), 7.98 (1H, dd, <i>J</i> 1.2, 7.4), 8.28-8.31 (2H, m), 8.34-8.38 (1H, m), 8.48 (1H, dd, <i>J</i> 2.5, 6.8), 8.55 (1H, d, <i>J</i> 2.0), 9.69 (1H, d, <i>J</i> 2.0).	312
15		5-[4-Fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine	7.54-7.68 (3H, m), 7.75-7.77 (2H, m), 8.21-8.25 (1H, m), 8.29-8.36 (3H, m), 8.60 (1H, d, <i>J</i> 2.3), 8.73-8.74 (2H, m), 9.73 (1H, d, <i>J</i> 2.3).	328
16		5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-phenylpyridazine	7.53-7.68 (5H, m), 7.92-7.97 (1H, m), 8.26-8.35 (4H, m), 8.55 (1H, d, <i>J</i> 2.3), 8.63-8.65 (1H, m), 9.67 (1H, d, <i>J</i> 2.3).	346

17		3-Phenyl-5-[3-(pyridin-2-ylmethoxy)phenyl]-pyridazine	5.33 (2H, s), 7.21-7.24 (1H, m), 7.30-7.40 (1H, m), 7.50-7.67 (6H, m), 7.76 (1H, t, <i>J</i> 2.0), 7.85-7.89 (1H, m), 8.29 (2H, d, <i>J</i> 1.6), 8.48 (1H, d, <i>J</i> 2.3), 8.60-8.65 (1H, m), 9.63 (1H, d, <i>J</i> 2.3).	340
18		5-[4-Fluoro-3-(3-fluoropyridin-4-yl)phenyl]-3-phenylpyridazine	7.54-7.68 (4H, m), 7.77 (1H, dd, <i>J</i> 5.1, 6.3), 8.29-8.36 (4H, m), 8.57 (1H, d, <i>J</i> 2.3), 8.63 (1H, dd, <i>J</i> 1.2, 5.1), 8.77 (1H, d, <i>J</i> 2.0), 9.71 (1H, d, <i>J</i> 2.3).	346
19		5-[2-Fluoro-3-(pyridin-4-yl)phenyl]-3-phenylpyridazine	7.50-7.71 (6H, m), 7.79-7.83 (1H, m), 7.94-7.99 (1H, m), 8.25-8.27 (2H, m), 8.48 (1H, dd, <i>J</i> 0.8, 1.2), 8.72-8.73 (2H, m), 9.53 (1H, t, <i>J</i> 2.0).	328
20		5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-phenylpyridazine	7.54-7.68 (4H, m), 8.16-8.22 (1H, m), 8.27-8.33 (4H, m), 8.54 (1H, d, <i>J</i> 2.0), 8.75 (1H, d, <i>J</i> 2.3), 9.66 (1H, d, <i>J</i> 2.3).	364

				
21		5-[4-Fluoro-3-(pyridin-3-yl)-phenyl]-3-phenylpyridazine	7.54-7.64 (5H, m), 8.13-8.22 (2H, m), 8.30-8.33 (3H, m), 8.60 (1H, d, <i>J</i> 2.5), 8.68 (1H, dd, <i>J</i> 1.6, 4.7), 8.94 (1H, s), 9.73 (1H, d, <i>J</i> 2.5).	328
22		[3-(6-Phenylpyridazin-4-yl)phenyl]acetonitrile		272
23		2-Fluoro-5-(6-phenylpyridazin-4-yl)benzonitrile		276
24		5-(3-Nitrophenyl)-3-phenylpyridazine		278
25		3-(6-Phenylpyridazin-4-yl)benzoic acid methyl ester		291

26		1-[3-(6-Phenylpyridazin-4-yl)-phenyl]-ethanone		275
27		5-(3-Fluorophenyl)-3-phenylpyridazine		251
28		3-Phenyl-5-(3-trifluoromethylphenyl)pyridazine		301
29		5-(3-Methoxyphenyl)-3-phenylpyridazine		263
30		5,2'-Difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile	7.54-7.80 (6H, m), 8.15-8.20 (1H, m), 8.29-8.36 (4H, m), 8.58 (1H, d, <i>J</i> 2.3), 9.72 (1H, d, <i>J</i> 2.3).	370
31		3,2'-Difluoro-5'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile	7.54-7.62 (3H, m), 7.65-7.71 (3H, m), 7.95-8.00 (1H, m), 8.29-8.38 (4H, m), 8.60-8.65 (1H, m), 9.70 (1H, d, <i>J</i> 2.4).	370
32		5-(4-Fluoro-3-	4.01 (3H, s), 7.25-7.27	281

		methoxy-phenyl)-3-phenyl-pyridazine	(3H, m), 7.52-7.58 (3H, m), 7.94 (1H, d, <i>J</i> 2.0), 8.15 (2H, dd, <i>J</i> 1.6, 7.8), 9.37 (1H, d, <i>J</i> 2.3).	
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EXAMPLE 33**6,2'-Difluoro-5'-[6-(4-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile**

5 5-Chloropyridazin-3-one (22 mg, 0.169 mmol), palladium bis-(diphenylphosphinylbutane)dichloride (10 mg), 6,2'-difluoro-5'-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)biphenyl-2-carbonitrile (50 mg, 0.15 mmol) and 2N Na₂CO₃ (0.3 ml) in toluene (3 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH₂Cl₂ (6 ml) and H₂O (2 ml) then poured into PTFE (5 μM) fritted syringe barrels. The organic phase was collected, concentrated and recrystallised from isopropanol to give 29 mg (62%) 6,2'-difluoro-5'-(6-oxo-1,6-dihydropyridazin-4-yl)biphenyl-2-carbonitrile.

10 The product from above was stirred with triethylamine (20 μl) and *N*-phenyltrifluoromethanesulfonimide (40 mg) in CH₂Cl₂ (5 ml) for 18 h. Further reagents were added and stirring continued for an additional 18 h. The reaction was concentrated and purified by column chromatography using 1:1 ethyl acetate/hexanes as eluent. Trifluoromethanesulfonic acid 5-(2'-cyano-6,6'-difluorobiphenyl-3-yl)pyridazin-3-yl ester was obtained as a yellow oil. *m/z* (ES⁺) 442.

15 The product from above, 4-fluorophenylboronic acid (14 mg), palladium bis(diphenylphosphinylbutane)dichloride (4 mg) and 2N Na₂CO₃ (0.5 ml) in tetrahydrofuran (2 ml) were combined and heated to 150°C for 600 s in a Smith Synthesiser microwave reactor. The reaction was diluted with CH₂Cl₂ (6 ml) and H₂O (2 ml) then poured into a PTFE (5

μM) fritted syringe barrel. The organic phase was collected, concentrated and purified by column chromatography using 1:1 ethyl acetate/hexanes as eluent. The *title compound* was recrystallised from isopropanol to give a colourless solid (3.9 mg). δ_{H} (400 MHz, d^6 DMSO) 7.42 (2H, t, J 8.8), 7.70 (1H, t, J 9.2), 7.76-7.87 (2H, m), 7.98 (1H, dd, J 1.0, 7.6), 8.34-8.39 (3H, m), 8.35-8.40 (1H, m), 8.45-8.48 (1H, m), 9.69 (1H, d, J 2.0); m/z (ES^+) 388.

EXAMPLE 34

10 4-Fluoro-3'-(6-phenylpyridazin-4-yl)biphenyl-2-carbonitrile

4-Fluoro-3'-(6-oxo-1,6-dihydropyridazin-4-yl)biphenyl-2-carbonitrile (0.35 g, 1.20 mmol) was suspended in phosphorus oxychloride (10 ml) and heated to 70°C for 1 h. The reaction was cooled to room temperature, poured onto ice water and stirred vigorously for 1 h. The beige solid was collected by filtration and azeotroped with methanol to give 3'-(6-chloropyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile (0.24 g). δ_{H} (400 MHz, d^6 DMSO) 7.73-7.82 (3H, m), 7.83-7.87 (1H, m), 8.04 (1H, dd, J 2.7, 9.0), 8.12 (1H, dt, J 1.6, 7.8), 8.22 (1H, t, J 1.6), 8.40 (1H, d, J 2.0), 9.77 (1H, d, J 2.0); m/z (ES^+) 310.

20 The product from above (40 mg, 0.129 mmol), benzenboronic acid (24 mg, 0.197 mmol), tetrakis(triphenylphosphine)palladium(0) and 2N Na_2CO_3 (0.5 ml) in tetrahydrofuran (1.5 ml) were combined and heated to 150°C for 10 min in a Smith Synthesiser microwave reactor. The reaction was diluted with CH_2Cl_2 (6 ml) and NH_4Cl (2 ml) then poured into a PTFE
25 (5 μM) fritted syringe barrel. The organic phase was concentrated while loading onto silica. Column chromatography using 40-50% ethyl acetate/hexanes gave the *title compound* as a white solid (20 mg). δ_{H} (400 MHz, d^6 DMSO) 7.56-7.62 (3H, m), 7.74-7.80 (3H, m), 7.85-7.89 (1H, m), 8.03-8.06 (1H, m), 8.19 (1H, dt, J 1.8, 7.0), 8.29-8.32 (3H, m), 8.58 (1H, d, J
30 2.0), 9.71 (1H, d, J 2.0); m/z (ES^+) 352.

EXAMPLES 35 TO 70

The compounds in Table 2 were prepared using the requisite boronic acids in an analogous manner to that described in Examples 33 and 34.

5

Table 2

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO unless specified otherwise)	m/z (ES ⁺)
35	6,2'-Difluoro-5'-[6-(thien-2-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.27 (1H, dd, J 4.7, 3.9), 7.71 (1H, t, J 9.2), 7.79-7.87 (3H, m), 7.97 (1H, d, J 7.0), 8.13 (1H, d, J 3.1), 8.33-8.35 (1H, m), 8.41 (1H, dd, J 1.2, 4.7), 8.59 (1H, d, J 1.2), 9.58 (1H, d, J 1.2).	376
36	6,2'-Difluoro-5'-[6-(4-methoxyphenyl)-pyridazin-4-yl]biphenyl-2-carbonitrile	3.86 (3H, s), 7.13 (2H, d, J 9.0), 7.69 (1H, t, J 9.2), 7.76-7.87 (2H, m), 7.97 (1H, dd, J 1.4, 7.6), 8.27 (2H, d, J 9.0), 8.32-8.36 (1H, m), 8.45 (1H, dd, J 2.3, 6.7), 8.48 (1H, d, J 2.0), 9.61 (1H, d, J 2.3).	400
37	5'-[6-(3-Chlorophenyl)-pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile	7.62-7.63 (2H, m), 7.69-7.73 (1H, m), 7.76-7.87 (2H, m), 7.96 (1H, d, J 1.6), 8.28-8.31 (1H, m), 8.36-8.40 (2H, m), 8.48 (1H, dd, J 2.5, 6.8), 8.62 (1H, d, J 2.0), 9.73 (1H, d, J	404

		2.3).	
38	6,2'-Difluoro-5'-[6-(pyridin-3-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.63 (1H, dd, <i>J</i> 4.7, 7.8), 7.70-7.88 (3H, m), 7.98 (1H, dd, <i>J</i> 1.2, 7.4), 8.36-8.40 (1H, m), 8.49 (1H, dd, <i>J</i> 2.3, 6.7), 8.64-8.68 (2H, m), 8.76 (1H, dd, <i>J</i> 1.2, 4.7), 9.45 (1H, d, <i>J</i> 1.6), 9.76 (1H, d, <i>J</i> 2.3).	371
39	5'-[6-(4-Chlorophenyl)pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile	7.56-7.92 (5H, m), 7.98 (1H, dd, <i>J</i> 1.2, 7.4), 8.28-8.50 (4H, m), 8.59 (1H, d, <i>J</i> 2.3), 9.71 (1H, d, <i>J</i> 2.3).	404
40	6,2'-Difluoro-5'-[6-(pyridin-4-yl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.70-7.88 (3H, m), 7.97 (1H, d, <i>J</i> 7.4), 8.28 (2H, dd, <i>J</i> 1.4, 4.5), 8.37-8.41 (1H, m), 8.49 (1H, dd, <i>J</i> 2.5, 6.8), 8.70 (1H, d, <i>J</i> 2.3), 8.81-8.84 (2H, m), 9.80 (1H, d, <i>J</i> 2.3).	371
41	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-fluorophenyl)pyridazine	7.42 (2H, t, <i>J</i> 9.0), 7.62 (1H, dd, <i>J</i> 8.6, 0.8), 8.17-8.22 (1H, m), 8.27-8.39 (4H, m), 8.55 (1H, d, <i>J</i> 2.3), 8.75 (1H, d, <i>J</i> 2.3), 9.66 (1H, d, <i>J</i> 2.3).	382
42	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(2-fluorophenyl)pyridazine	7.41-7.46 (2H, m), 7.53-7.66 (3H, m), 7.91-8.02 (2H, m), 8.20-8.27 (2H, m), 8.37 (1H, t, <i>J</i> 2.0), 8.63-8.64 (1H, m), 9.72 (1H, d, <i>J</i> 2.3).	364

43	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)pyridazine	(CDCl ₃): 7.20-7.24 (1H, m), 7.34-7.41 (3H, m), 7.47-7.53 (1H, m), 7.80-7.84 (1H, m), 7.96 (1H, dd, <i>J</i> 2.3, 6.7), 8.13 (1H, t, <i>J</i> 2.0), 8.19-8.24 (1H, m), 8.52 (1H, d, <i>J</i> 2.3), 9.44 (1H, d, <i>J</i> 2.0).	382
44	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-3-yl)pyridazine	7.60-7.67 (3H, m), 7.92-7.97 (1H, m), 8.28-8.38 (2H, m), 8.64-8.68 (3H, m), 8.76 (1H, dd, <i>J</i> 1.6, 4.7), 9.46 (1H, d, <i>J</i> 2.0), 9.74 (1H, d, <i>J</i> 2.0).	347
45	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluorophenyl)pyridazine	(CDCl ₃): 7.20-7.25 (1H, m), 7.36-7.43 (2H, m), 7.50-7.55 (1H, m), 7.81-8.00 (5H, m), 8.52 (1H, d, <i>J</i> 2.3), 9.45 (1H, d, <i>J</i> 2.0).	382
46	3-(2,4-Difluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-pyridazine	(CDCl ₃): 6.96-7.02 (1H, m), 7.08-7.13 (1H, m), 7.36-7.42 (2H, m), 7.79-7.83 (1H, m), 7.95 (1H, dd, <i>J</i> 2.3, 6.3), 8.09 (1H, t, <i>J</i> 2.2), 8.23-8.29 (1H, m), 8.52 (1H, d, <i>J</i> 2.3), 9.44 (1H, d, <i>J</i> 2.3).	400
47	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-methoxyphenyl)-pyridazine	(CDCl ₃): 3.93 (3H, s), 7.06-7.09 (1H, m), 7.36-7.47 (3H, m), 7.64 (1H, d, <i>J</i> 1.6), 7.79-7.84 (2H, m), 7.97 (1H, dd, <i>J</i> 2.3, 6.7), 8.01 (1H, d, <i>J</i> 2.3),	394

		8.52 (1H, d, <i>J</i> 2.3), 9.43 (1H, d, <i>J</i> 2.3).	
48	6,2'-Difluoro-5'-[6-(2-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.41-7.46 (2H, m), 7.59-7.72 (2H, m), 7.75-7.86 (2H, m), 7.94-8.01 (2H, m), 8.27-8.31 (1H, m), 8.39 (2H, q, <i>J</i> 2.1), 9.73 (1H, d, <i>J</i> 2.3).	388
49	6,2'-Difluoro-5'-[6-(3-fluorophenyl)pyridazin-4-yl]biphenyl-2-carbonitrile	7.38-7.43 (1H, m), 7.61-7.88 (4H, m), 7.96-8.05 (1H, m), 8.13-8.19 (2H, m), 8.35-8.40 (1H, m), 8.48 (1H, dd, <i>J</i> 2.5, 6.7), 8.61 (1H, d, <i>J</i> 2.1), 9.73 (1H, d, <i>J</i> 1.8).	388
50	3-[6-(3-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.40-7.45 (1H, m), 7.66 (1H, td, <i>J</i> 6.3, 8.0), 7.81 (1H, t, <i>J</i> 7.8), 8.04 (1H, dt, <i>J</i> 1.2, 7.8), 8.15-8.19 (1H, m), 8.19-8.22 (1H, m), 8.42-8.45 (1H, m), 8.66 (1H, m), 8.67 (1H, d, <i>J</i> 2.3), 9.74 (1H, d, <i>J</i> 2.3).	276
51	3-[6-(2-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.43-7.48 (2H, m), 7.60-7.66 (1H, m), 7.80 (1H, t, <i>J</i> 7.8), 7.98-8.02 (1H, m), 8.02-8.04 (1H, m), 8.34-8.37 (1H, m), 8.42 (1H, t, <i>J</i> 2.0), 8.56-8.57 (1H, m), 9.75 (1H, d, <i>J</i> 2.0).	276
52	3-[6-(4-Fluorophenyl)-pyridazin-4-yl]-benzonitrile	7.41-7.47 (2H, m), 7.81 (1H, t, <i>J</i> 7.8), 8.02-8.05 (1H, m), 8.37-8.41 (2H, m), 8.41-8.49 (1H, m), 8.62 (1H, d, <i>J</i> 2.0),	276

		8.64-8.65 (1H, m), 9.70 (1H, d, <i>J</i> 2.0).	
53	3-[6-(4-Methoxyphenyl)-pyridazin-4-yl]-benzonitrile	3.87 (3H, s), 7.13-7.16 (2H, m), 7.80 (1H, t, <i>J</i> 7.8), 8.01-8.04 (1H, m), 8.28-8.31 (2H, m), 8.39-8.42 (1H, m), 8.54 (1H, d, <i>J</i> 2.0), 8.62-8.64 (1H, m), 9.62 (1H, d, <i>J</i> 2.0).	288
54	3-[6-(3,4-Difluorophenyl)pyridazin-4-yl]-benzonitrile	7.69 (1H, td, <i>J</i> 8.6, 10.6), 7.82 (1H, t, <i>J</i> 7.8), 8.03-8.06 (1H, m), 8.22-8.26 (1H, m), 8.39-8.42 (1H, m), 8.42-8.45 (1H, m), 8.65-8.66 (1H, m), 8.66 (1H, d, <i>J</i> 2.0), 9.73 (1H, d, <i>J</i> 2.0).	294
55	3-[6-(2,4-Difluorophenyl)pyridazin-4-yl]-benzonitrile	7.33-7.38 (1H, m), 7.50-7.56 (1H, m), 7.80 (1H, t, <i>J</i> 7.8), 8.20-8.05 (1H, m), 8.08 (1H, td, <i>J</i> 7.0, 9.0), 8.34-8.37 (1H, m), 8.41 (1H, t, <i>J</i> 2.0), 8.55-8.57 (1H, m), 9.75 (1H, d, <i>J</i> 2.0).	294
56	5'-[6-(2-Chlorophenyl)-pyridazin-4-yl]-6,2'-difluorobiphenyl-2-carbonitrile	7.60-7.65 (2H, m), 7.73 (1H, t, <i>J</i> 9.1), 7.78-7.90 (2H, m), 7.98-8.05 (1H, m), 8.33 (2H, dd, <i>J</i> 1.9, 7.5), 8.36-8.41 (1H, m), 8.50 (1H, dd, <i>J</i> 2.3, 6.8), 8.58 (1H, d, <i>J</i> 2.1), 9.72 (1H, d, <i>J</i> 2.1).	
57	3-(4-Methoxyphenyl)-5-	3.86 (3H, s), 7.13 (2H, d, <i>J</i>	

	phenylpyridazine	8.9), 7.56-7.62 (3H, m), 8.02-8.05 (2H, m), 8.25 (2H, d, <i>J</i> 8.9), 8.39 (1H, d, <i>J</i> 2.1), 9.53 (1H, d, <i>J</i> 2.1).	
58	4-Fluoro-3'-[6-(4-methoxy-phenyl)pyridazin-4-yl]-biphenyl-2-carbonitrile	3.86 (3H, s), 7.14 (2H, d, <i>J</i> 8.8), 7.73-7.79 (3H, m), 7.85-7.89 (1H, m), 8.03-8.06 (1H, m), 8.17 (1H, dt, <i>J</i> 2.0, 7.0), 8.27-8.28 (1H, m), 8.28 (2H, d, <i>J</i> 8.8), 8.51 (1H, d, <i>J</i> 2.3), 9.63 (1H, d, <i>J</i> 2.3).	382
59	5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(4-methoxyphenyl)-pyridazine	(CDCl ₃): 3.90 (3H, s), 7.07 (2H, d, <i>J</i> 9.0), 7.36-7.41 (2H, m), 7.79-7.82 (1H, m), 7.94-7.96 (2H, m), 8.13 (1H, q, <i>J</i> 5.0), 8.12 (1H, d, <i>J</i> 9.0), 8.52 (1H, d, <i>J</i> 2.3), 9.36 (1H, d, <i>J</i> 2.3).	394
60	3-(4-Chlorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-pyridazine	7.62-7.67 (3H, m), 8.17-8.22 (1H, m), 8.27-8.36 (4H, m), 8.58 (1H, d, <i>J</i> 2.0), 8.75 (1H, d, <i>J</i> 2.3), 9.68 (1H, d, <i>J</i> 2.3).	398
61	2-{5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]pyridazin-3-yl}-5-fluorobenzonitrile	(CDCl ₃): 7.36-7.45 (2H, m), 7.50-7.59 (2H, m), 7.84-7.87 (1H, m), 7.99 (1H, dd, <i>J</i> 2.3, 6.3), 8.15 (1H, dd, <i>J</i> 5.5, 8.6), 8.18 (1H, d, <i>J</i> 2.0), 8.51 (1H, d, <i>J</i> 2.3), 9.54 (1H, d, <i>J</i> 2.3).	398
62	3-(4-Chlorophenyl)-5-[4-	(CDCl ₃): 7.38-7.46 (2H, m),	380

	fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine	7.52-7.61 (3H, m), 7.80-7.84 (1H, m), 8.00 (1H, d, <i>J</i> 1.6), 8.01 (1H, d, <i>J</i> 2.3), 8.11 (2H, d, <i>J</i> 8.2), 8.60 (1H, d, <i>J</i> 4.3), 9.44 (1H, d, <i>J</i> 2.0).	
63	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-3-yl)pyridazine	(CDCl ₃): 7.08-7.10 (1H, m), 7.36-7.46 (2H, m), 7.55-7.61 (2H, m), 7.76-7.81 (2H, m), 7.98 (1H, dd, <i>J</i> 2.5, 6.5), 8.23 (1H, s), 8.59-8.61 (1H, m), 9.34 (1H, d, <i>J</i> 2.3).	336
64	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(furan-2-yl)pyridazine	(CDCl ₃): 6.63 (1H, q, <i>J</i> 1.8), 7.36-7.45 (3H, m), 7.55-7.60 (1H, m), 7.63-7.64 (1H, m), 7.80-7.84 (1H, m), 8.01 (1H, dd, <i>J</i> 2.5, 6.5), 8.04 (1H, d, <i>J</i> 2.0), 8.59-8.61 (1H, m), 9.34 (1H, d, <i>J</i> 2.3).	336
65	3-(2,3-Difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine	(CDCl ₃): 7.24-7.45 (4H, m), 7.52-7.60 (1H, m), 7.80-7.84 (1H, m), 7.94-8.02 (2H, m), 8.13 (1H, t, <i>J</i> 2.2), 8.59-8.61 (1H, m), 9.48 (1H, d, <i>J</i> 2.0).	382
66	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thien-3-yl)pyridazine	(CDCl ₃): 7.37-7.52 (3H, m), 7.55-7.61 (1H, m), 7.79-7.83 (1H, m), 7.86 (1H, dd, <i>J</i> 1.2, 5.1), 7.92 (1H, d, <i>J</i> 2.3), 7.99 (1H, dd, <i>J</i> 2.3, 6.3), 8.14 (1H, q, <i>J</i> 1.4), 8.59-8.61 (1H, m),	352

		9.37 (1H, d, <i>J</i> 2.0).	
67	5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-3-(thien-2-yl)pyridazine	(CDCl ₃): 7.19 (1H, dd, <i>J</i> 3.7, 4.9), 7.37-7.46 (2H, m), 7.52-7.61 (2H, m), 7.77-7.82 (2H, m), 7.94 (1H, d, <i>J</i> 2.3), 7.99 (1H, dd, <i>J</i> 2.5, 6.5), 8.59-8.61 (1H, m), 9.33 (1H, d, <i>J</i> 2.0).	352
68	3-(2,5-Difluorophenyl)-5-[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazine	(CDCl ₃): 7.14-7.23 (2H, m), 7.37-7.45 (2H, m), 7.52-7.60 (1H, m), 7.80-7.84 (1H, m), 7.96-8.01 (2H, m), 8.16 (1H, t, <i>J</i> 2.2), 8.59-8.61 (1H, m), 9.47 (1H, d, <i>J</i> 2.3).	382
69	3-(3,4-Difluorophenyl)-5-[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazine	(CDCl ₃): 7.31-7.46 (3H, m), 7.56-7.61 (1H, m), 7.80-7.84 (1H, m), 7.87-7.91 (1H, m), 7.97-8.09 (3H, m), 8.59-8.61 (1H, m), 9.45 (1H, d, <i>J</i> 2.3).	382
70	4-{5-[4-Fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]-pyridazin-3-yl}-benzonitrile	(CDCl ₃): 7.39-7.47 (2H, m), 7.57-7.61 (1H, m), 7.82-7.87 (3H, m), 8.03 (1H, dd, <i>J</i> 2.5, 6.5), 8.06 (1H, d, <i>J</i> 2.0), 8.28 (1H, s), 8.30 (1H, t, <i>J</i> 1.8), 8.59-8.61 (1H, m), 9.51 (1H, d, <i>J</i> 2.3).	371

EXAMPLE 71***N*-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-methylamine**

5

Lead tetraacetate (363.3 g, 819 mmol) and trifluoroacetic acid (825 ml) were combined and cooled to 0°C before adding 1-bromo-3-

vinylbenzene (150 g, 819 mmol) in CH_2Cl_2 (1 l) dropwise so as to maintain a temperature of $<10^\circ\text{C}$. The reaction was then allowed to warm to room temperature and stirred for 2 h. The reaction was diluted with CH_2Cl_2 (500 ml), poured into H_2O (3 l), and stirred vigorously before filtering through a pad of Hyflo. The organic phase was separated and the cake rinsed with a further portion of CH_2Cl_2 (1 l), which was subsequently washed with the separated aqueous phase. The combined organic extracts were washed with H_2O (750 ml), NaHCO_3 (750 ml) and H_2O (750 ml), dried over MgSO_4 and concentrated to give (3-bromophenyl)acetaldehyde (163 g), which was used directly.

6N HCl (139 ml) was added dropwise to a solution of morpholine (75 ml, 860 mmol) in 1,4-dioxane (1140 ml). On complete addition, glyoxylic acid (72 g, 778 mmol) and the product from above (163 g, 819 mmol) were added and the reaction heated to reflux for 15 h. The reaction was cooled to room temperature, diluted with H_2O (800 ml) and the products extracted into ethyl acetate (2 x 800 ml). The combined organic extracts were washed with brine (125 ml), dried over MgSO_4 and concentrated. 4-(3-Bromophenyl)-5-hydroxy-5*H*-furan-2-one was obtained as a cream solid by crystallising from diethyl ether/hexanes (95.6 g). δ_{H} (360 MHz, d^6 DMSO) 6.64 (1H, d, J 8.8), 6.88 (1H, s), 7.48 (1H, t, J 8.1), 7.70-7.73 (1H, m), 7.78-7.81 (1H, m), 8.00-8.01 (1H, m), 8.04 (1H, d, J 8.8).

The product from above (95.6 g, 375 mmol) and hydrazine hydrate (45.5 ml, 937 mmol) in ethanol (1.9 l) were combined and heated to reflux for 12 h. The reaction was cooled to room temperature, diluted with H_2O (960 ml) and cooled in an ice bath. 5-(3-Bromophenyl)-2*H*-pyridazin-3-one was obtained as a pale yellow solid, which was collected by filtration (34 g). The filtrate was concentrated to a smaller volume and a further 16 g of product was collected by filtration. δ_{H} (360 MHz, d^6 DMSO) 7.20 (1H, d, J 2.1), 7.48 (1H, t, J 7.9), 7.70-7.73 (1H, m), 7.81-7.84 (1H, m), 8.04 (1H, t, J 1.8), 8.30 (1H, d, J 2.1), 13.15 (1H, s).

The product from above (10 g, 39.8 mmol) was suspended in phosphorus oxychloride (60 ml) and heated to 70°C for 3 h. The reaction was concentrated to half the volume before pouring onto ice water and stirring vigorously for 1 h. 5-(3-Bromophenyl)-3-chloropyridazine was obtained as an orange solid, which was collected by filtration and azeotroped with toluene (10.6 g). δ_H (360 MHz, d_6 DMSO) 7.54 (1H, t, J 7.9), 7.76-7.79 (1H, m), 7.99-8.02 (1H, m), 8.25 (1H, t, J 1.8), 8.35 (1H, d, J 2.1), 9.70 (1H, d, J 2.1).

The product from above (0.5 g, 1.86 mmol) was added to a 2M solution of methylamine in tetrahydrofuran (3 ml) and heated to 170°C for 1 h in a Smith Synthesiser microwave reactor. The organic phase was diluted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated while loading onto silica. Column chromatography using 50% ethyl acetate/hexanes followed by ethyl acetate as eluent gave the *title compound* as an orange solid (0.1 g). δ_H (360 MHz, d_6 DMSO) 2.92 (3H, d, J 4.9), 6.85 (1H, q, J 4.9), 7.00 (1H, d, J 2.1), 7.49 (1H, t, J 7.9), 7.68-7.71 (1H, m), 7.75-7.78 (1H, m), 7.97 (1H, t, J 1.8), 8.80 (1H, d, J 2.1); m/z (ES^+) 264, 266.

EXAMPLES 72 TO 78

The compounds in Table 3 were prepared in an analogous manner to that described in Example 71.

Table 3

EX. NO.	PRODUCT	δ_H (400 MHz, d_6 DMSO)	m/z (ES^+)
72	<i>N</i> -[5-(3-Bromophenyl)-pyridazin-3-yl]- <i>N</i> -	1.21 (6H, d, J 6.3), 4.13-4.22 (1H, m), 6.70 (1H, d, J 7.4), 6.97 (1H, d, J 2.1), 7.49 (1H, t, J 7.9),	292, 294

	isopropylamine	7.68-7.71 (1H, m), 7.72-7.75 (1H, m), 7.93 (1H, t, <i>J</i> 1.8), 8.76 (1H, d, <i>J</i> 2.1).	
73	<i>N</i> -[5-(3-Bromophenyl)-pyridazin-3-yl]- <i>N</i> -cyclopropylamine	0.47-0.51 (2H, m), 0.75-0.80 (2H, m), 2.65-2.73 (1H, m), 7.08 (1H, d, <i>J</i> 2.0), 7.33-7.35 (1H, m), 7.50 (1H, t, <i>J</i> 7.9), 7.69-7.72 (1H, m), 7.77-7.80 (1H, m), 7.99 (1H, t, <i>J</i> 1.8), 8.86 (1H, d, <i>J</i> 2.0).	290, 292
74	<i>N</i> -Allyl- <i>N</i> -[5-(3-bromophenyl)-pyridazin-3-yl]amine	4.04-4.08 (2H, m), 5.10-5.13 (1H, m), 5.22-5.28 (1H, m), 5.93-6.02 (1H, m), 7.04 (1H, d, <i>J</i> 2.0), 7.05-7.07 (1H, m), 7.49 (1H, t, <i>J</i> 7.8), 7.68-7.71 (1H, m), 7.74-7.77 (1H, m), 7.95 (1H, t, <i>J</i> 1.8), 8.82 (1H, d, <i>J</i> 2.0).	290, 292
75	<i>N</i> -[5-(3-Bromophenyl)-pyridazin-3-yl]- <i>N</i> -ethylamine	1.20 (3H, t, <i>J</i> 7.0), 3.41 (2H, qd, <i>J</i> 5.5, 7.0), 6.84 (1H, t, <i>J</i> 5.5), 6.99 (1H, d, <i>J</i> 2.0), 7.49 (1H, t, 7.8), 7.68-7.71 (1H, m), 7.74-7.77 (1H, m), 7.95 (1H, t, <i>J</i> 1.8), 8.79 (1H, d, <i>J</i> 2.0).	278, 280
76	<i>N</i> -Benzyl- <i>N</i> -[5-(3-bromophenyl)-pyridazin-3-yl]amine	4.64 (2H, d, <i>J</i> 5.9), 7.08 (1H, d, <i>J</i> 2.0), 7.22-7.26 (1H, m), 7.31-7.35 (2H, m), 7.37-7.42 (3H, m), 7.49 (1H, t, 7.8), 7.68-7.71 (1H, m), 7.73-7.76 (1H, m), 7.94 (1H, t, <i>J</i> 2.0), 8.82 (1H, d, <i>J</i> 2.0).	340, 342

77	<i>N</i> -[5-(3-Bromophenyl)-pyridazin-3-yl]- <i>N</i> -(2-methoxybenzyl)-amine	3.85 (3H, s), 4.59 (2H, d, <i>J</i> 5.9), 6.87-6.91 (1H, m), 7.00-7.03 (1H, m), 7.11 (1H, d, <i>J</i> 2.0), 7.18 (1H, t, <i>J</i> 5.9), 7.22-7.29 (2H, m), 7.49 (1H, t, <i>J</i> 7.8), 7.68-7.71 (1H, m), 7.73-7.76 (1H, m), 7.93-7.94 (1H, m), 8.81 (1H, d, <i>J</i> 2.0).	370, 372
78	5-(3-Bromophenyl)-3-(2,5-dihydropyrrol-1-yl)pyridazine	4.36 (4H, s), 6.09 (2H, s), 7.11 (1H, d, <i>J</i> 2.0), 7.50 (1H, t, <i>J</i> 7.8), 7.69-7.72 (1H, m), 7.87-7.90 (1H, m), 8.12 (1H, t, <i>J</i> 1.8), 8.90 (1H, d, <i>J</i> 2.0).	302, 304

EXAMPLE 79

5-(3-Bromophenyl)-3-ethoxypyridazine

5 Sodium metal (0.13 g, 5.65 mmol) was added portionwise to dry ethanol (10 ml) under external cooling (water bath). On addition of all the sodium, the reaction was allowed to attain room temperature and the solution stirred for 1 h before adding 5-(3-bromophenyl)-3-chloropyridazine (0.15 g, 0.557 mmol) in ethanol (5 ml). The suspension was stirred for 18 h

10 before adding water and removing the ethanol *in vacuo*. The products were extracted into CH₂Cl₂, dried over MgSO₄ and concentrated. The *title compound* was obtained as a white solid following preparative TLC using 25% ethyl acetate/hexanes as eluent (30 mg). δ_{H} (400 MHz, d⁶ DMSO) 1.41 (3H, t, *J* 7.0), 4.55 (2H, q, *J* 7.0), 7.50 (1H, t, *J* 8.0), 7.55 (1H, d, *J* 2.0),

15 7.71-7.74 (1H, m), 7.91-7.94 (1H, m), 8.14 (1H, t, *J* 1.8), 9.30 (1H, d, *J* 2.0); *m/z* (ES⁺) 279, 281.

EXAMPLE 80**3-Allyloxy-5-(3-bromophenyl)pyridazine**

Sodium hydride as a 60% dispersion in mineral oil (0.175 g, 4.38 mmol) was added to a solution of allyl alcohol (0.25 ml, 3.79 mmol) in tetrahydrofuran (4 ml) and stirred for 30 min before adding 5-(3-bromophenyl)-3-chloropyridazine (0.5 g, 1.86 mmol). The suspension was heated to 170°C for 30 min in a Smith Synthesiser microwave reactor. The reaction was diluted with ethyl acetate, washed with H₂O, dried over MgSO₄ and concentrated while loading onto silica. Column chromatography using 20% ethyl acetate/hexanes as eluent gave the *title compound* as a white solid (0.2 g). δ_H (400 MHz, d⁶ DMSO) 5.03-5.05 (2H, m), 5.29-5.32 (1H, m), 5.44-5.50 (1H, m), 6.10-6.20 (1H, m), 7.51 (1H, t, *J* 8.0), 7.61 (1H, d, *J* 2.0), 7.72-7.75 (1H, m), 7.92-7.95 (1H, m), 8.16 (1H, t, *J* 1.8), 9.33 (1H, d, *J* 2.0); *m/z* (ES⁺) 291, 293.

EXAMPLE 81**3-(6-Isopropylaminopyridazin-4-yl)benzonitrile**

N-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-isopropylamine (0.1 g, 0.342 mmol), zinc cyanide (52 mg, 0.443 mmol) and tetrakis(triphenylphosphine)palladium(0) (10 mg) were taken up in *N,N*-dimethylformamide (2 ml). The reaction was heated to 150°C for 10 min in a Smith Synthesiser microwave reactor. The reaction was diluted with CH₂Cl₂ (6 ml) and H₂O (2 ml) then poured into a PTFE (5 μ M) fritted syringe barrel. The organic phase was concentrated and purified by column chromatography using 50-75% ethyl acetate/hexanes as eluent. The *title compound* was obtained as a white solid by recrystallising from ethyl acetate (36 mg). δ_H (400 MHz, d⁶ DMSO) 1.21 (6H, d, *J* 6.7), 4.13-4.21 (1H, m), 6.76 (1H, d, *J* 7.4), 7.01 (1H, d, *J* 2.0), 7.74 (1H, t, *J* 7.8), 7.95-7.97 (1H, m), 8.05-8.08 (1H, m), 8.25-8.26 (1H, m), 8.81 (1H, d, *J* 2.0); *m/z* (ES⁺) 238.

EXAMPLES 82 TO 84

5 The compounds in Table 4 were prepared in an analogous manner to that described in Example 81.

Table 4

EX. NO.	PRODUCT	δ_H (400 MHz, d^6 DMSO)	m/z (ES ⁺)
82	3-(6-Benzylamino-pyridazin-4-yl)-benzonitrile	4.65 (2H, d, J 5.9), 7.13 (1H, d, J 1.6), 7.22-7.26 (1H, m), 7.31-7.35 (2H, m), 7.38-7.40 (2H, m), 7.47 (1H, t, J 5.9), 7.74 (1H, t, J 7.8), 7.94-7.97 (1H, m), 8.06-8.09 (1H, m), 8.26-8.28 (1H, m), 8.87 (1H, d, J 1.6).	287
83	3-[6-(2-Methoxybenzylamino)-pyridazin-4-yl]-benzonitrile	3.84 (3H, s), 4.60 (2H, d, J 5.9), 6.87-6.91 (1H, m), 7.00-7.03 (1H, m), 7.16 (1H, d, J 2.0), 7.22-7.28 (3H, m), 7.74 (1H, t, J 7.8), 7.95-7.97 (1H, m), 8.06-8.09 (1H, m), 8.26-8.27 (1H, m), 8.86 (1H, d, J 2.0).	317
84	3-(6-Benzyloxy-pyridazin-4-yl)-benzonitrile	5.59 (2H, s), 7.34-7.38 (1H, m), 7.40-7.44 (2H, m), 7.52-7.55 (2H, m), 7.72 (1H, d, J 2.0), 7.76 (1H, t, J 7.8), 7.98-8.01 (1H, m), 8.26-8.29 (1H, m), 8.46-8.47 (1H, m), 9.40 (1H, d,	288

		<i>J</i> 2.0).	
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EXAMPLE 85**3'-(6-Ethylaminopyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile**

- 5 *N*-[5-(3-Bromophenyl)pyridazin-3-yl]-*N*-ethylamine (0.1 g, 0.360 mmol), 2-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)-5-fluorobenzonitrile (0.1 g, 0.429 mmol), 2N Na₂CO₃ (0.5 ml) and tetrakis(triphenylphosphine)-palladium(0) (10 mg) in tetrahydrofuran (1.5 ml) were combined and heated to 150°C for 10 min in a Smith Synthesiser microwave reactor.
- 10 The reaction was diluted with CH₂Cl₂ (6 ml) and NH₄Cl (2 ml) then poured into a PTFE (5 μM) fritted syringe barrel. The organic phase was concentrated while loading onto silica and purified by column chromatography using 50% ethyl acetate/hexanes followed by ethyl acetate as eluent. The *title compound* was obtained as a white solid by
- 15 recrystallising from ethyl acetate (46 mg). δ_H (400 MHz, d⁶ DMSO) 1.19 (3H, t, *J* 7.0), 3.41 (2H, qd, *J* 5.1, 7.0), 6.88 (1H, t, *J* 5.1), 7.05 (1H, d, *J* 1.6), 7.69-7.76 (3H, m), 7.79-7.83 (1H, m), 7.85-7.88 (1H, m), 7.94-7.95 (1H, m), 8.01-8.04 (1H, m), 8.85 (1H, d, *J* 1.6); *m/z* (ES⁺) 319.

20

EXAMPLES 86 TO 94

The compounds in Table 5 were prepared in an analogous manner to that described in Example 85.

25

Table 5

EX. NO.	PRODUCT	δ _H (400 MHz, d ⁶ DMSO)	<i>m/z</i> (ES ⁺)
86	4-Fluoro-3'-(6-isopropylamino-	1.21 (6H, d, <i>J</i> 6.3), 4.14-4.22 (1H, m), 6.74 (1H, d, <i>J</i> 7.8), 7.03	333

	pyridazin-4-yl)- biphenyl-2-carbonitrile	(1H, d, <i>J</i> 2.0), 7.69-7.76 (3H, m), 7.79-7.82 (1H, m), 7.84-7.86 (1H, m), 7.92-7.94 (1H, m), 8.01- 8.04 (1H, m), 8.83 (1H, d, <i>J</i> 2.0).	
87	4-Fluoro-3'-(6- propylaminopyridazin- 4-yl)biphenyl-2- carbonitrile	0.95 (3H, d, <i>J</i> 7.2), 1.56-1.67 (2H, m), 3.33-3.37 (2H, m), 6.89- 6.93 (1H, m), 7.06-7.07 (1H, m), 7.69-7.88 (5H, m), 7.93-7.95 (1H, m), 8.00-8.04 (1H, m), 8.84- 8.85 (1H, m).	333
88	3'-(6-Cyclopropyl- aminopyridazin-4-yl)- 4-fluorobiphenyl-2- carbonitrile	0.48-0.52 (2H, m), 0.75-0.80 (2H, m), 2.65-2.71 (1H, m), 7.16 (1H, d, <i>J</i> 2.0), 7.35-7.37 (1H, m), 7.70-7.76 (3H, m), 7.80-7.84 (1H, m), 7.88-7.91 (1H, m), 7.98- 7.99 (1H, m), 8.01-8.04 (1H, m), 8.92 (1H, d, <i>J</i> 2.0).	331
89	3'-(6-Allylamino- pyridazin-4-yl)-4- fluorobiphenyl-2- carbonitrile	4.04-4.07 (2H, m), 5.09-5.13 (1H, m), 5.23-5.28 (1H, m), 5.93- 6.02 (1H, m), 7.07-7.09 (1H, m), 7.10 (1H, d, <i>J</i> 1.6), 7.70-7.76 (3H, m), 7.79-7.83 (1H, m), 7.85- 7.88 (1H, m), 7.94-7.95 (1H, m), 8.01-8.04 (1H, m), 8.80 (1H, d, <i>J</i> 1.6).	331
90	3'-(6-Benzylamino- pyridazin-4-yl)-4- fluorobiphenyl-2- carbonitrile	4.64 (2H, d, <i>J</i> 5.9), 7.14 (1H, d, <i>J</i> 2.0), 7.22-7.26 (1H, m), 7.31- 7.35 (2H, m), 7.38-7.41 (2H, m), 7.45 (1H, t, <i>J</i> 5.2), 7.69-7.76 (3H, m), 7.78-7.82 (1H, m), 7.84- 7.87 (1H, m), 7.92-7.94 (1H, m),	381

		8.01-8.04 (1H, m), 8.89 (1H, d, <i>J</i> 2.0).	
91	4-Fluoro-3'-(6-methylamino-pyridazin-4-yl)-biphenyl-2-carbonitrile	2.92 (3H, d, <i>J</i> 5.1), 6.88 (1H, t, <i>J</i> 5.1), 7.06 (1H, d, <i>J</i> 2.0), 7.69-7.76 (3H, m), 7.79-7.83 (1H, m), 7.86-7.89 (1H, m), 7.95-7.96 (1H, m), 8.00-8.04 (1H, m), 8.87 (1H, d, <i>J</i> 2.0).	305
92	4-Fluoro-3'-(6-methoxypyridazin-4-yl)biphenyl-2-carbonitrile	4.09 (3H, s), 7.61 (1H, d, <i>J</i> 2.0), 7.70-7.77 (3H, m), 7.82-7.86 (1H, m), 8.01-8.04 (2H, m), 8.13 (1H, t, <i>J</i> 1.6), 9.39 (1H, d, <i>J</i> 2.0).	306
93	3'-(6-Ethoxypyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	1.42 (3H, t, <i>J</i> 7.0), 4.55 (2H, q, <i>J</i> 7.0), 7.59 (1H, d, <i>J</i> 2.0), 7.70-7.77 (3H, m), 7.83-7.86 (1H, m), 8.01-8.04 (2H, m), 8.13-8.14 (1H, m), 9.37 (1H, d, <i>J</i> 2.0).	320
94	3'-(6-Benzoyloxy-pyridazin-4-yl)-4-fluorobiphenyl-2-carbonitrile	5.59 (2H, s), 7.34-7.44 (3H, m), 7.52-7.55 (2H, m), 7.70 (1H, d, <i>J</i> 2.0), 7.71-7.77 (3H, m), 7.82-7.86 (1H, m), 8.01-8.06 (2H, m), 8.14-8.15 (1H, m), 9.41 (1H, d, <i>J</i> 2.0).	382

EXAMPLE 95**5-(4-Fluoro-3-hydroxyphenyl)-3-phenylpyridazine**

5

To a solution of 5-(4-fluoro-3-methoxyphenyl)-3-phenylpyridazine (0.6 g, 2.14 mmol) in dichloromethane cooled to -70°C was added boron tribromide (0.81 ml, 8.56 mmol). The reaction mixture was stirred at

-70°C for 30 min then allowed to warm to room temperature and stirred for 2 h. The reaction was cooled to 0°C, then 1 ml of methanol was added. The reaction mixture was poured onto a solution of sodium hydrogencarbonate, the precipitate obtained was collected by filtration, washed with water and dried (MgSO₄) to give the *title compound* (400 mg). δ_{H} (400 MHz, CDCl₃) 7.37 (1H, dd, *J* 8.4, 11.2), 7.47-7.61 (5H, m), 8.26-8.28 (2H, m), 8.37 (1H, d, *J* 2.0), 9.50 (1H, d, *J* 2.0), 10.25-10.40 (1H, br s); *m/z* (ES⁺) 267.

10

EXAMPLE 96

5-[4-Fluoro-3-(2-methyl-2H-[1,2,4]triazol-3-ylmethoxy)phenyl]-3-phenylpyridazine

To a solution of 5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine (80 mg, 0.3 mmol) in *N,N*-dimethylformamide (2 ml) was added sodium hydride (30 mg, 0.6 mmol). After stirring for 10 min (2-methyl-2H-[1,2,4]triazol-3-yl)methanol (50 mg, 0.3 mmol) was added. The reaction mixture was heated at 60°C for 30 min. The reaction mixture was poured into water, and the precipitate obtained was collected by filtration, washed with water and dried (MgSO₄). The solid was dissolved in ethyl acetate, adsorbed onto silica and purified by flash chromatography using ethyl acetate/hexane (20:1) as eluent. The appropriate fractions were combined and evaporated under reduced pressure to give the *title compound* as a solid. δ_{H} (400 MHz, CDCl₃) 4.05 (3H, s), 5.44 (2H, s), 7.27-7.37 (3H, m), 7.51-7.61 (3H, m), 7.92 (2H, dd, *J* 11.3, 2.3), 8.16 (2H, dd, *J* 6.3, 1.6), 9.34 (1H, d, *J* 1.6); *m/z* (ES⁺) 362.

30

EXAMPLE 97

5-[4-Fluoro-3-(1-methyl-3-trifluoromethyl-1H-pyrazol-4-ylmethoxy)-phenyl]-3-phenylpyridazine

To a slurry of 5-(4-fluoro-3-hydroxyphenyl)-3-phenylpyridazine (80 mg, 0.3 mmol), (1-methyl-3-trifluoromethyl-1*H*-pyrazol-4-yl)methanol (81 mg, 0.45 mmol) and triphenylphosphine (118 mg, 0.45 mmol) in tetrahydrofuran (2 ml) was added diisopropyl azodicarboxylate (91 mg, 0.45 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adsorbed onto silica and purified by flash chromatography using a gradient elution of isohexane/ethyl acetate 20:1 to 1:20 as eluent. The appropriate fractions were combined and evaporated under reduced pressure to give a solid which was recrystallized from acetonitrile to give the *title compound* (45 mg). δ_{H} (400 MHz, CDCl_3) 3.96 (3H, s), 5.21 (2H, s), 7.27-7.34 (3H, m), 7.51-7.61 (4H, m), 7.91 (1H, d, *J* 2.3), 8.13-8.14 (2H, m), 9.35 (1H, d, *J* 2.3); *m/z* (ES^+) 429.

EXAMPLES 98 AND 99

The compounds in Table 6 were prepared in an analogous manner to that described in Example 96.

Table 6

EX. NO.	PRODUCT	δ_{H} (400 MHz, CDCl_3)	<i>m/z</i> (ES^+)
98	5-[4-Fluoro-3-(pyridin-4-ylmethoxy)phenyl]-3-phenylpyridazine	5.27 (2H, s), 7.28-7.34 (3H, m), 7.42 (2H, d, <i>J</i> 6.3), 7.51-7.59 (3H, m), 7.88 (1H, d, <i>J</i> 2.0), 8.11-8.13 (2H, m), 8.66-8.68 (2H, m), 9.32 (1H, d, <i>J</i> 2.0).	358
99	5-[4-Fluoro-3-(pyridin-3-ylmethoxy)phenyl]-3-phenylpyridazine	5.26 (2H, s), 7.27-7.39 (4H, m), 7.51-7.59 (3H, m), 7.83-7.86 (1H, m), 7.90 (1H, d, <i>J</i> 2.3), 8.12-8.14 (2H, m), 8.63 (1H, d, <i>J</i> 3.9), 8.74	358

	(1H, s), 9.33 (1H, d, <i>J</i> 2.0).	
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EXAMPLE 100**5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-4-yl)pyridazine**

5 To 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (0.2 g, 0.66 mmol) in 1,4-dioxane (2 ml) was added 4-tri-*n*-butylstannylpyridine (0.484 g, 1.31 mmol) followed by tetrakis(triphenylphosphine)palladium(0) (0.076 g, 0.065 mmol) and the mixture heated at 150°C in a Smith

10 Synthesiser microwave reactor for 12 min. The reaction was diluted with dichloromethane, filtered and evaporated to give a brown solid. The crude product was chromatographed on silica eluting with 1-5%

methanol/CH₂Cl₂. Appropriate fractions were pooled and evaporated to give the *title compound* as a cream-coloured solid. δ_H (400 MHz, CDCl₃) 7.40-7.47 (2H, m), 7.57-7.61 (1H, m), 7.82-7.86 (1H, m), 8.02-8.09 (4H, m),

15 8.60-8.62 (1H, m), 8.82-8.84 (2H, m), 9.53 (1H, d, *J* 2.3); *m/z* (ES⁺) 347.

EXAMPLES 101 TO 104

20 The compounds in Table 7 were prepared using the requisite heterocyclic stannanes in an analogous manner to that described in Example 100 above.

Table 7

EX. NO.	PRODUCT	δ_H (400 MHz, CDCl ₃)	<i>m/z</i> (ES ⁺)
101	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-	7.38-7.46 (2H, m), 7.56-7.61 (1H, m), 7.87-7.92 (1H, m), 8.09 (1H, dd, <i>J</i> 2.3, 6.7), 8.59 (1H, m), 8.68-	348

	(pyrazin-2-yl)-pyridazine	8.75 (3H, m), 9.55 (1H, d, <i>J</i> 2.3), 9.97 (1H, d, <i>J</i> 1.2).	
102	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(thiazol-2-yl)pyridazine	7.37-7.46 (2H, m), 7.55-7.61 (2H, m), 7.86-7.90 (1H, m), 8.02 (1H, d, <i>J</i> 3.5), 8.08 (1H, dd, <i>J</i> 2.3, 6.7), 8.56 (1H, d, <i>J</i> 2.3), 8.59-8.61 (1H, m), 9.49 (1H, d, <i>J</i> 2.3).	353
103	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(pyridin-2-yl)pyridazine	7.54-7.67 (3H, m), 7.92-7.97 (1H, m), 8.05-8.09 (1H, m), 8.24 (1H, s), 8.26 (1H, s), 8.61-8.66 (2H, m), 8.78 (1H, d, <i>J</i> 2.3), 8.80 (1H, dd, <i>J</i> 0.8, 4.3), 9.77 (1H, d, <i>J</i> 2.3).	347
104	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-4-yl)pyridazine	7.39-7.46 (2H, m), 7.56-7.61 (1H, m), 7.81-7.85 (1H, m), 8.02 (1H, dd, <i>J</i> 2.5, 6.5), 8.23 (2H, s), 8.60 (1H, d, <i>J</i> 4.3), 8.67 (2H, dd, <i>J</i> 0.8, 7.0), 9.54 (1H, d, <i>J</i> 1.6).	365

EXAMPLE 105

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(1*H*-[1,2,3]triazol-4-yl)pyridazine

5

A degassed solution of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (200 mg, 0.66 mmol) was formed in tetrahydrofuran (3 ml). (Trimethylsilyl)acetylene (0.14 ml, 0.99 mmol), triethylamine (0.14 ml, 1 mmol), bis(triphenylphosphine)palladium(II) chloride (23 mg, 0.03 mmol) and triphenylphosphine (4 mg, 0.015 mmol) were added in that order and the mixture left to stir for 20 min at room temperature.

10

Copper(I) iodide (2 mg, 0.01 mmol) was added and the mixture stirred at room temperature for 18 h. The solvent was removed and the residue purified by flash column chromatography over silica using 80% ethyl

acetate:20% isohexane as eluent to give 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-trimethylsilanylethynylpyridazine as a brown solid (210 mg). δ_{H} (400 MHz, CDCl_3) 0.31 (9H, s), 7.34-7.45 (2H, m), 7.55-7.60 (1H, m), 7.74-7.78 (1H, m), 7.79 (1H, d, J 2.3), 7.95 (1H, dd, J 2.5, 6.5), 8.58-8.61 (1H, m), 9.39 (1H, d, J 2.3).

Sodium azide (19 mg, 0.29 mmol) was added to a solution of 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-trimethylsilanylethynylpyridazine (100 mg, 0.26 mmol) in N,N -dimethylformamide (1 ml) and the mixture stirred at room temperature for 16 h, then at 70°C for 4 h. The reaction mixture was allowed to cool to room temperature and was added to water (20 ml) then extracted with ethyl acetate (5 x 10 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to a brown solid. Purification by preparative thin-layer chromatography using 10% methanol:90% dichloromethane as eluent gave the *title compound* as a tan solid. δ_{H} (400 MHz, d^6 -DMSO) 7.63 (1H, t, J 9.8), 8.16-8.27 (3H, m), 8.49 (1H, d, J 2.3), 8.69 (1H, s), 8.75 (1H, d, J 2.3), 9.66 (1H, d, J 2.0); m/z (ES^+) 355.

EXAMPLE 106

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine-3-carboxylic acid ethyl ester

A solution of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (100 mg, 0.33 mmol) was formed in ethanol (10 ml) with N,N -dimethylformamide (2 ml). Sodium acetate (54 mg, 0.66 mmol) was added and the mixture degassed with nitrogen. [1,1'-Bis(diphenylphosphino)-ferrocene]palladium(II) chloride (1:1 complex with dichloromethane) (20 mg, 0.03 mmol) was added and carbon dioxide was bubbled through the solution as the mixture was heated to 90°C and maintained at that temperature for 45 min. The mixture was allowed to cool to room temperature and the solvent was removed. The residue was purified by

flash column chromatography over silica, using 80% ethyl acetate:20% isohexane as eluent, then recrystallisation from dichloromethane and isohexane, to give the *title compound* as a white solid (30 mg). δ_H (400 MHz, $CDCl_3$) 1.51 (3H, t, J 7.0), 4.59 (2H, q, J 7.2), 7.38-7.46 (2H, m), 7.55-7.61 (1H, m), 7.81-7.86 (1H, m), 8.03 (1H, dd, J 2.5, 6.5), 8.41 (1H, d, J 2.3), 8.59-8.61 (1H, m), 9.62 (1H, d, J 2.3); m/z (ES⁺) 342.

EXAMPLE 107

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)-pyridazine-1-oxide

To a mixture of 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluorophenyl)pyridazine (50 mg, 0.13 mmol) in CH_2Cl_2 (2 ml) was added *m*-chloroperbenzoic acid (50%; 68 mg, 0.20 mmol). The solution was left to stand at room temperature for 22 h. 10% Sodium carbonate solution (1 ml) was added and the solution poured into a PTFE (5 μ M) fritted syringe barrel. The organic phase was evaporated and the crude product purified by preparative TLC using a solvent system of 5% methanol in CH_2Cl_2 to yield a white solid. The solid was further purified by prep HPLC using a solvent system of 30-80% acetonitrile in 0.1% trifluoroacetic acid in water. Appropriate fractions were combined to give the *title compound* as a white solid (3 mg). δ_H (400 MHz, $CDCl_3$) 7.19-7.25 (1H, m), 7.29-7.41 (3H, m), 7.47-7.53 (1H, m), 7.73-7.76 (1H, m), 7.78 (1H, t, J 1), 7.91 (1H, dd, J 3, 7), 8.06-8.10 (1H, m), 8.42 (1H, d, J 1), 8.51 (1H, d, J 2); m/z (ES⁺) 398.

EXAMPLE 108

3-(2,6-Difluorophenyl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine

To a degassed mixture of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (0.25 g, 0.82 mmol), hexamethylditin (0.323 g, 0.98 mmol) and lithium chloride (0.1024 g, 2.46 mmol) in 1,4-dioxane (12 ml)

was added tetrakis(triphenylphosphine)palladium(0) (0.048 g, 0.041 mmol) and the mixture heated at 100°C for 3 h. Mass spectroscopy showed formation of the intended stannane. 1-Bromo-2,6-difluorobenzene (0.3177 g, 0.187 ml, 1.65 mmol) was added, followed by tetrakis(triphenylphosphine)palladium(0) (0.01 g, 0.0082 mmol), and the mixture heated at 100°C for 6 h. The reaction was cooled to room temperature, filtered and evaporated and the crude product purified by preparative TLC (2 plates; 4% methanol-CH₂Cl₂). Appropriate bands were collected and processed to give the *title compound* as an off-white solid which was recrystallised from ethyl acetate/isohexane to give a white solid (42 mg). δ_H (400 MHz, CDCl₃) 7.05-7.12 (2H, m), 7.32-7.59 (4H, m), 7.79-7.85 (2H, m), 8.00 (1H, dd, *J* 2.5, 6.5), 8.58-8.60 (1H, m), 9.51 (1H, d, *J* 2.3).

EXAMPLE 109

3-(4-Chloro-2-fluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine

3-Chloro-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine was coupled to 1-bromo-4-chloro-2-fluorobenzene by the method of Example 108 to give 3-(4-chloro-2-fluorophenyl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine as a white solid: δ_H (500 MHz, DMSO) 7.54 (1H, m), 7.61-7.65 (1H, m), 7.70 (1H, dd, *J* 10.0, 0.5), 8.03-8.06 (1H, m), 8.16-8.24 (3H, m), 8.37 (1H, s), 8.74 (1H, s), 9.73 (1H, s); *m/z* (ES⁺) 416:418 (3:1).

EXAMPLE 110

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-trifluoromethylphenyl)pyridazine

3-Chloro-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine was coupled to 4-bromo-3-fluorobenzotrifluoride by the method of Example 108 to give 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-trifluoromethylphenyl)pyridazine as a white solid: δ_H (500 MHz, DMSO) 7.64 (1H, t, J 9.0), 7.82 (1H, d, J 8.1), 7.95 (1H, d, J 10.5), 8.16-8.26 (3H, m), 8.24 (1H, s), 8.46 (1H, s), 8.74 (1H, s), 9.78 (1H, s); m/z (ES⁺) 450.

EXAMPLE 111

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-methylphenyl)-pyridazine

3-Chloro-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine was coupled to 4-bromo-3-fluorotoluene by the method of Example 108 to give 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-methylphenyl)pyridazine as a white solid: δ_H (500 MHz, DMSO) 2.42 (3H, s), 7.25 (2H, s), 7.62 (1H, t, J 9.4), 7.93 (1H, m), 8.21 (3H, m), 8.30 (1H, s), 8.74 (1H, d, J 0.5), 9.68 (1H, s); m/z (ES⁺) 396.

EXAMPLE 112

3-(3,5-Difluoropyridin-2-yl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine

3-Chloro-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine was coupled to 2-bromo-3,5-difluoropyridine by the method of Example 108 to give 3-(3,5-difluoropyridin-2-yl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine as a white solid: δ_H (500 MHz, DMSO) 7.61-7.65 (1H, m), 8.16-8.24 (4H, m), 8.48 (1H, s), 8.75 (2H, d, J 12.2), 9.79 (1H, s); m/z (ES⁺) 401.

EXAMPLE 113**Trifluoromethanesulfonic acid 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazin-3-yl ester**

5 A suspension of 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-2*H*-pyridazin-3-one (1.29 g, 4.52 mmol) was formed in dry pyridine (20 ml) and cooled to 0°C. Trifluoromethanesulfonic anhydride (1.14 ml, 6.78 mmol) was added dropwise. The mixture was then allowed to warm to room temperature and after 30 min formed a dark red solution. The
10 mixture was poured into water (100 ml) and extracted with dichloromethane (2 x 100 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to a brown solid. Purification by flash column chromatography over silica using 80% dichloromethane:20% ethyl acetate as eluent then recrystallization from
15 dichloromethane using isohexane gave trifluoromethanesulfonic acid 5-[4-fluoro-3-(3-fluoro-pyridin-2-yl)phenyl]pyridazin-3-yl ester as a white solid: δ_H (400 MHz, CDCl₃) 7.40-7.47 (2H, m), 7.56-7.61 (2H, m), 7.78-7.82 (1H, m), 8.00 (1H, dd, *J* 2 and 6), 8.59-8.61 (1H, m), 9.55 (1H, d, *J* 2); *m/z* (ES⁺) 418.

20

EXAMPLE 114**3-Ethylsulfanyl-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine**

25 A solution of 3-chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-pyridazine (50 mg, 0.16 mmol) was formed in *N,N*-dimethylformamide (1 ml). Sodium ethanethiolate (28 mg, 0.33 mmol) was added and the mixture stirred at room temperature for 8 h. The reaction was poured into water (20 ml) and extracted with ethyl acetate (2 x 20 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and
30 evaporated to an orange solid. Purification by preparative thin layer chromatography using ethyl acetate as eluent gave 3-ethylsulfanyl-5-[4-

fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine as a white solid (10 mg): δ_{H} (400 MHz, CDCl_3) 1.47 (3H, t, J 7), 3.43 (2H, q, J 7), 7.35 (1H, t, J 9), 7.40-7.44 (1H, m), 7.48 (1H, d, J 2), 7.54-7.59 (1H, m), 7.70-7.74 (1H, m), 7.92 (1H, dd, J 2 and 6), 8.57-8.60 (1H, m), 9.17 (1H, d, J 2); m/z (ES^+) 330.

5

EXAMPLE 115

3-tert-Butylsulfanyl-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine

3-Chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (50 mg, 0.16 mmol) and sodium 2-methyl-2-propanethiolate (37 mg, 0.33 mmol) were reacted as in Example 114 to give 3-tert-butylsulfanyl-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine as a tan solid (13 mg): δ_{H} (400 MHz, CDCl_3) 1.66 (9H, s), 7.35 (1H, t, J 9), 7.40-7.44 (1H, m), 7.53 (1H, d, J 2), 7.54-7.59 (1H, m), 7.70-7.74 (1H, m), 7.91 (1H, dd, J 3 and 7), 8.58-8.60 (1H, m), 9.21 (1H, d, J 2); m/z (ES^+) 302 ($\text{M}+\text{H}-t\text{Bu}$) and 358 ($\text{M}+\text{H}$).

15

EXAMPLE 116

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluoropyridin-4-yl)-pyridazine

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25

3-Chloro-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine (100 mg, 0.31 mmol) was coupled to 3-fluoro-4-tributylstannylpyridine (144 mg, 0.37 mmol) using the method in Example 100 to give 5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluoropyridin-4-yl)pyridazine as a white solid (31 mg): δ_{H} (400 MHz, CDCl_3) 7.36-7.44 (2H, m), 7.81-7.85 (1H, m), 7.97 (1H, dd, J 2 and 7), 8.21-8.24 (2H, m), 8.52 (1H, d, J 2), 8.64-8.68 (2H, m), 9.53 (1H, d, J 2); m/z (ES^+) 383.

5-[3-(3,5-Difluoropyridin-2-yl)-4-fluorophenyl]-3-(3-fluoropyridin-2-yl)-
pyridazine

EXAMPLE 118

3-Chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (216 mg, 0.71 mmol) was coupled to 3-fluoro-2-tributylstannylpyridine (300 mg, 0.78 mmol) using the method in Example 100 to give 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-2-yl)pyridazine as a white solid (106 mg): δ_H (400 MHz, $CDCl_3$) 7.35-7.48 (3H, m), 7.55-7.61 (1H, m), 7.63-7.68 (1H, m), 7.84-7.89 (1H, m), 8.05 (1H, dd, J 3 and 7), 8.41 (1H, d, J 2), 8.58-8.62 (2H, m), 9.54 (1H, d, J 2); m/z (ES⁺) 365.

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-4-yl)-pyridazine 1-oxide

A solution of 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoro-
30 pyridin-4-yl)pyridazine (100 mg, 0.27 mmol) was formed in
dichloromethane (4 ml). A solution of *m*-chloroperoxybenzoic acid (74 mg,

77%, 0.33 mmol) in dichloromethane (1 ml) was added and the mixture stirred at room temperature overnight. The reaction was quenched into aqueous sodium carbonate (2M, 10 ml) and extracted with dichloromethane (10 ml). The organic phase was washed with aqueous sodium carbonate (1M, 2 x 10 ml) then dried over anhydrous magnesium sulphate, filtered and evaporated to a tan solid. Purification by preparative HPLC gave 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoropyridin-4-yl)pyridazine 1-oxide as a white solid (14 mg): δ_H (400 MHz, $CDCl_3$) 7.39-7.47 (2H, m), 7.56-7.61 (1H, m), 7.74-7.78 (1H, m), 7.86 (1H, s), 7.96 (1H, dd, *J* 3 and 7), 8.02 (1H, t, *J* 5), 8.49 (1H, d, *J* 1), 8.58-8.68 (3H, m); *m/z* (ES^+) 381.

EXAMPLE 120

5-[4-Fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoro-1-oxypyridin-4-yl)-pyridazine

A solution of 3-fluoro-4-tributylstannylpyridine (1.0 g, 2.6 mmol) was formed in dichloromethane (5 ml). A solution of *m*-chloroperoxybenzoic acid (696 mg, 77%, 3.1 mmol) in dichloromethane (3 ml) was added and the mixture stirred at room temperature for 2 h. A further 10 ml of dichloromethane was added and the mixture was washed with saturated aqueous sodium bicarbonate (2 x 20 ml) then dried over anhydrous magnesium sulphate, filtered and evaporated to a yellow oil. Purification by flash column chromatography over silica using ethyl acetate as eluent gave 3-fluoro-4-tributylstannylpyridine 1-oxide as a colourless oil (1.0 g).

3-Chloro-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine (80 mg, 0.26 mmol) was coupled to 3-fluoro-4-tributylstannylpyridine 1-oxide (117 mg, 0.29 mmol) using the method in Example 100 to give 5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]-3-(3-fluoro-1-oxypyridin-4-yl)pyridazine as a tan solid (31 mg): δ_H (400 MHz, $CDCl_3$) 7.39-7.47 (2H, m), 7.56-7.62 (1H, m), 7.80-7.84 (1H, m), 8.00 (1H, dd, *J* 3 and 7), 8.18-8.22 (2H, m); 8.29 (1H,

dd, *J* 2 and 7), 8.39 (1H, dd, *J* 7 and 9), 8.59-8.61 (1H, m), 9.50 (1H, d, *J* 2); *m/z* (ES⁺) 381.

EXAMPLE 121

5

5-[2,4-Difluoro-3-(3,5-difluoropyridin-2-yl)phenyl]-3-(3,5-difluoropyridin-4-yl)pyridazine

A degassed solution of 2-bromo-3,5-difluoropyridine (4.0 g, 20.6 mmol), 2,6-difluorophenylboronic acid (3.9 g, 24.7 mmol) and potassium fluoride (4.3 g, 74.2 mmol) was formed in tetrahydrofuran (40 ml) with
10 water (4 ml). Tris(dibenzylideneacetone)dipalladium(0) (189 mg, 0.21 mmol) followed by tri-*tert*-butylphosphine (0.8 ml, 0.51M in hexane, 0.42 mmol) were added and the mixture heated to 60°C for 18 h. The solvent was removed and the residue purified by flash column chromatography.
15 over silica using dichloromethane 60%:isohexane 40% as eluent to give 3,5-difluoro-2-(2,6-difluorophenyl)pyridine as a white solid (2.2 g): δ_H (400 MHz, CDCl₃) 6.99-7.06 (2H, m), 7.32-7.46 (2H, m), 8.50 (1H, d, *J* 2.3).

A solution of 3,5-difluoro-2-(2,6-difluorophenyl)pyridine (1.65 g, 7.26 mmol) was formed in concentrated sulphuric acid (10 ml) and cooled to
20 0°C. 1,3-Dibromo-5,5-dimethylhydantoin (2.08 g, 7.26 mmol) was added portionwise and the mixture left to stir at 0°C for 2 h. The reaction was quenched into ice (250 ml) and extracted with dichloromethane (2 x 100 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to a yellow oil. Purification by flash
25 column chromatography over silica using 60% isohexane:40% dichloromethane as eluent gave 2-(3-bromo-2,6-difluorophenyl)-3,5-difluoropyridine as a colourless oil (1.95 g): δ_H (400 MHz, CDCl₃) 6.94-6.99 (1H, m), 7.34-7.39 (1H, m), 7.61-7.67 (1H, m), 8.50 (1H, d, *J* 2.3).

A degassed solution of 2-(3-bromo-2,6-difluorophenyl)-3,5-difluoropyridine (1.95 g, 6.37 mmol), bis(neopentyl glycolato)diborane (1.58
30 g, 7.01 mmol) and potassium acetate (1.25 g, 12.7 mmol) was formed in

1,4-dioxane (20 ml) with dimethylsulphoxide (0.4 ml). [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (100 mg) was added and the mixture heated at 80°C for 18 h. The solvent was removed and the residue stirred with aqueous sodium hydroxide (2N, 100 ml) for 30 min, then filtered. The filtrate was washed with diethyl ether (2 x 50 ml) then cooled to 0°C before being neutralised with concentrated aqueous hydrochloric acid, then extracted with dichloromethane (2 x 50 ml). The combined organics were dried over anhydrous magnesium sulphate, filtered and evaporated to give 3,5-difluoro-2-[2,6-difluoro-3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl]pyridine as a pale yellow oil: δ_H (400 MHz, $CDCl_3$) 1.03 (6H, s), 3.78 (4H, s), 5.30 (1H, s), 6.97-7.02 (1H, m), 7.29-7.35 (1H, m), 7.80-7.86 (1H, m), 8.48 (1H, d, J 2.3).

A degassed solution of 3-chloro-5-methoxypyridazine (473 mg, 3.27 mmol), 3,5-difluoro-4-trimethylstannanylpuridine (1.0 g, 3.6 mmol), copper(I) iodide (31 mg, 0.2 mmol) and lithium chloride (416 mg, 9.8 mmol) was formed in 1,4-dioxane (10 ml). Tetrakis(triphenylphosphine)-palladium(0) (100 mg) was added and the mixture heated to 80°C for 16 h. The solvent was removed and the residue was purified by flash column chromatography over silica using 40% isohexane:60% ethyl acetate to give 3-(3,5-difluoropyridin-4-yl)-5-methoxypyridazine as a pale yellow solid (220 mg): δ_H (400 MHz, $CDCl_3$) 7.10-7.12 (1H, m), 8.54 (2H, s), 9.02 (1H, d, J 3.1); m/z (ES^+) 224.

A solution of 3-(3,5-difluoropyridin-4-yl)-5-methoxypyridazine (210 mg, 0.94 mmol) was formed in aqueous hydrobromic acid (5 ml, 48%) and refluxed for 2 h. The mixture was cooled in an ice bath and neutralised with aqueous sodium hydroxide to ~ pH 2 then with solid sodium hydrogencarbonate to neutral. The resulting white precipitate was filtered and dried under vacuum over phosphorus pentoxide to give 6-(3,5-difluoropyridin-4-yl)-1H-pyridazin-4-one as a white solid (110 mg): m/z (ES^+) 210.

A suspension of 6-(3,5-difluoropyridin-4-yl)-1*H*-pyridazin-4-one (60 mg, 0.28 mmol) was formed in phosphorus oxychloride (0.8 ml) and heated to 80°C for 30 min to give a yellow solution. The phosphorus oxychloride was removed under reduced pressure and the residue diluted with
5 dichloromethane (5 ml) and washed with water (3 x 10 ml) and saturated aqueous sodium hydrogencarbonate (10 ml) then dried over anhydrous magnesium sulphate, filtered and evaporated to give 5-chloro-3-(3,5-difluoropyridin-4-yl)pyridazine as a yellow solid (63 mg): δ_H (400 MHz, CDCl₃) 7.76-7.78 (1H, m), 8.58 (2H, s), 9.31 (1H, d, *J* 2.3).

10 A solution of 5-chloro-3-(3,5-difluoropyridin-4-yl)pyridazine (107 mg, 0.47 mmol) and 3,5-difluoro-2-[2,6-difluoro-3-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)phenyl]pyridine (191 mg, 0.56 mmol) was formed in 1,4-dioxane (4 ml) with aqueous sodium carbonate (1 ml, 2 M). Tetrakis(triphenylphosphine)palladium(0) (50 mg) was added and the
15 mixture heated to 150°C for 700 s in a Smith Synthesiser microwave reactor. The solvent was evaporated and the residue purified by flash column chromatography over silica using dichloromethane:ethyl acetate (1:1). Recrystallization from dichloromethane using isohexane gave 5-[2,4-difluoro-3-(3,5-difluoropyridin-2-yl)phenyl]-3-(3,5-difluoropyridin-4-
20 yl)pyridazine as a white solid (106 mg): δ_H (400 MHz, CDCl₃) 7.25-7.29 (1H, m), 7.38-7.43 (1H, m), 7.66-7.72 (1H, m), 7.90-7.91 (1H, m), 8.54 (1H, d, *J* 2.3), 8.57 (2H, s), 9.50-9.51 (1H, m); *m/z* (ES⁺) 419.

EXAMPLES 122 AND 123

25 The compounds in Table 2A were prepared using the requisite boronic acids in an analogous manner to that described in Examples 33 and 34.

Table 2A

EX. NO.	PRODUCT	δ_H	m/z (ES⁺)
122	5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]-3-(2-fluoro-4-methoxyphenyl)-pyridazine	(500 MHz, DMSO): 3.98 (3H, s), 7.42 (1H, s), 7.65 (1H, dd, <i>J</i> 8.7, 9.2), 7.89-7.91 (1H, m), 8.05 (1H, d, <i>J</i> 8.1), 8.17-8.21 (1H, m), 8.29 (1H, s), 8.30 (1H, s), 8.55 (1H, s), 8.75 (1H, s), 9.65 (1H, s).	412
123	5-[4-Fluoro-3-(3-fluoropyridin-2-yl)-phenyl]-3-(2-fluoro-4-methoxyphenyl)-pyridazine	(400 MHz, CDCl ₃): 3.89 (3H, s), 6.77 (1H, dd, <i>J</i> 2.3, 13.3), 6.91 (1H, dd, <i>J</i> 2.3, 8.6), 7.36-7.44 (2H, m), 7.55-7.60 (1H, m), 7.79-7.82 (1H, m), 7.99 (1H, dd, <i>J</i> 2.3, 6.7), 8.10 (1H, t, <i>J</i> 2.0), 8.21 (1H, t, <i>J</i> 9.0), 8.58-8.60 (1H, m), 9.39 (1H, d, <i>J</i> 2.0).	394

EXAMPLES 124 TO 126

5

The compounds in Table 7A were prepared using the requisite heterocyclic stannanes in an analogous manner to that described in Example 100.

Table 7A

EX. NO.	PRODUCT	δ_H	m/z (ES ⁺)
124	3-(3,5-Difluoropyridin-4-yl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine	(400 MHz, d ₆ DMSO) 7.63-7.68 (2H, m), 7.95 (1H, m), 8.23-8.29 (2H, m), 8.55 (1H, br s), 8.64 (1H, m), 8.81 (2H, s), 9.88 (1H, d, <i>J</i> 1.8).	383
125	3-(3,5-Difluoropyridin-2-yl)-5-[4-fluoro-3-(3-fluoropyridin-2-yl)phenyl]pyridazine	(400 MHz, d ₆ DMSO) 7.61-7.67 (2H, m), 7.95 (1H, m), 8.22-8.27 (3H, m), 8.49 (1H, d, <i>J</i> 1.8), 8.65 (1H, m), 8.77 (1H, d, <i>J</i> 1.8), 9.81 (1H, d, <i>J</i> 1.9).	383
126	3-(3,5-Difluoropyridin-4-yl)-5-[3-(3,5-difluoropyridin-2-yl)-4-fluorophenyl]pyridazine	(400 MHz, CDCl ₃): 7.36-7.43 (2H, m), 7.80-7.84 (1H, m), 7.89 (1H, t, <i>J</i> 1.0), 7.97 (1H, dd, <i>J</i> 2.3, 6.7), 8.51 (1H, d, <i>J</i> 2.3), 8.57 (2H, s), 9.57 (1H, d, <i>J</i> 2.3).	401

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